Review Article

# Role of Parasites in Cancer

[1]Mandong BM, [2]Ngbea JA, [1]Raymond Vhriterhire
[1]Department of Pathology University of Jos
[2]Department of Pathology College of Health Sciences Benue State University, Markudi Benue State

**ABSTRACT**
**BACKGROUND**: In areas of parasitic endemicity, the occurrence of cancer that is not frequent may be linked with parasitic infection. Epidemiological correlates between some parasitic infections and cancer is strong, suggesting a strong aetiological association. The common parasites associated with human cancers are schistosomiasis, malaria, liver flukes (*Clonorchis sinenses, Opistorchis viverrini*).
**OBJECTIVE**: To review the pathology, literature and methods of diagnosis.
**METHOD**: Literature review from peer reviewed Journals cited in *PubMed* and local journals.
**CONCLUSION**: Parasites may serve as promoters of cancer in endemic areas of infection.
**KEY WORD**: parasites; cancers; schistosomiasis; liver flukes

**Date Accepted for Publication:** 16th March, 2013
NigerJMed 2013: 89-92


## INTRODUCTION

The intensity of parasitic infection frequency correlates with its prevalence; thus when cancer occurs in endemic areas of parasite infection strong suspicion is raised on its correlations. In the tropics, parasitic infestation is endemic and presents a big challenge to public health.[1,2,3,4]

Eradication of parasites through deworming, good sanitary habit and good water supply is associated with improved quality of health and probably reduction in parasitic associated cancer especially, schistosomiasis and urinary bladder cancer[(5).]

The data associating schistosomiasis and urinary bladder cancer are overwhelming but a direct causal relationship is lacking[5,6].

In tropical Africa and other developing nations, squamous cell carcinoma of the bladder is associated with schistosomiasis in endemic areas. In these areas of poor resource environment, local irrigation practice and man's contact with the risk factors of schistosomal infection increase the frequency of squamous cell carcinoma[6,7].

In Egypt the association between schistosomal infection seems to be stronger with long standing severe infection[7]. The age and sex frequencies show that more males are affected and mortality rates estimated to occur in the 5th decade. This contrast with transitional cell carcinoma that is more common in 6th and seventh decades[6,7]. There is no documented prospective study measuring the risk of urinary bladder cancer and schistosomal infection. However, if this is to be established, Koch's postulation must be fulfilled;

(1) That the worm must produce carcinogenic agent
(2) It must carry a carcinogenic virus or
(3) Co-carcinogene that would add insult to urinary bladder epithelium.

### Pathogenesis

The pathogenesis of urinary bladder schistosomal carcinogenesis is correlated with prolonged infection, squamous metaplasia of transitional cells, co-infection and activation of metabolites related N-nitroso compounds. These carcinogens are also expressed in urinary infection, in which nitrites and N-nitroso compounds excretion are increased in schistosomal infection [8,9,10]. The prevalence of urinary nitrites in symptomatic patient who also have schistosomal cancer has been observed to be increased significantly [8]. In non-schistosomal urinary bladder cancer, infection with schistosomal haematobium increases significantly the ability of the vesical bacterial flora to reduce nitrates to nitrites which precursors of N-nitroso compounds[9]

When compared to controls, schistosomiasis patients have a threefold increase in urinary nitrate and it seems possible that this resulted from increased synthesis of nitric oxide by inflammatory cells.[10,11]. The endogenous production of nitric oxide and alkylation of DNA by N-nitroso compound formed by reaction of nitrite with urinary secondary amines could account for the significant excess of transitions at CpG dinucleotide in p53 gene in urinary bladder cancer, when compared with the non-schistosomal urinary bladder cancer." [10].

It has been suggested that inactivation of p53 could be responsible for the conversion of low-grade tumour to an invasive one [11,12]. The detection of multiple p53 mutation in invasive bladder cancer of squamous cell variety is suggestive of the involvement of a carcinogenic agent with maintenance of preferential activation of the HRAS gene[11,12].

HRAS gene codes for proteins involved in signal

Correspondence: P.O. BOX 887, Email: mafala2004@yahoo.com.

transduction and is frequently mutated in urinary bladder cancers in about 40% of cases[13]. Urinary tract infection is associated with increased chromosomal breakage in the urothelium in patients with urinary bladder cancer. The frequency of micronuclei (these are microRNAs that are involved in gene regulation. They do not code for any protein but instead, inhibit gene expression) is significantly reduced after deworming. [10]

Urothelial carcinogenesis in the presence of schistosomiasis seems to proceed along a different pathway from those linked to cigarette smoking which appears to have significant impact on mutation of the p53 gene with A:T to G.C transitions that are not observed in schistosomal bladder cancer[10,12]. The latter also displays p16INK4a (cell cycle inhibitor) alteration, more frequently than other bladder tumours[12].

Schistosomiasis induces chronic granulomatous reaction with formation cystits glandularis and squamous metaplasia; cystis glandularies may predispose to adenocarcinoma.

In non-schistosomiasis related bladder cancer, the tumour frequently arises from the trigone areas. However, schistosomiasis related bladder cancers arise frequently in areas remote from the ureters, mostly in the anterior and posterior bladder wall[11]. This peculiarity tends to strengthen its association with schistosomal infection because the scanty or altogether absent submucosal tissue of the trigone discourages significant deposition of ova[11,12].

**Histological classification:**
In most African countries squamous cell carcinomas accounts for over 60 per cent of urinary bladder cancer. In Nigeria the figures may rise from 50 per cent to 80 per cent in some centres [1,2]

This is understanbly because of schistosoma endemicity is most common in resource poor communities. It is also established that the more intense the infection, the greater is the proportion of squamous cell cancer with a reciprocal decrease in the frequency of transitional cell cancers. [7]

Metabolic observation of patients with schisostomasis show increase urinary excretion of free 3 hydroxykynurenine, 3 hydroxyanthranilic acid and 2 amino-3-hydroxyacetophenone in schistosomiasis induced squamous cell carcinoma.[11,12]

These orthoaminophenol derivatives of tryptophan are generally excreted as conjugates of sulfuric acid or glucuronic acid. They are related to the carcinogenic metabolites of P-Naphthylamine and are themselves carcinogenic to mice[13].

**Schistosomiasis and colon cancer**:
In the tropics, with schistosomal endemicity, the relationship between colon cancer and schithosomiasis remains speculative. However, in some far eastern countries of Asia, there appears to be causal relationship between schistosomiasis and colorectal carcinoma.[12, 14]

**Distomiasis**
Liver fluke infections have been associated with multifocal intrahepatic bile duct adenocarcinoma in those areas of Asia where distomiasis is endemic like Thailand, where 70-90 per cent of the population is infected with *Opisthorchis viverrini*. This place has the highest record of cholangiocarcinomas in the world[15]. *Opisthorchis viverrini* is endemc in Japan, Korea and China[15, 16]. In these areas of liver fluke endemicity, cholangiocarcinoma accounts for 20% of liver cancers.

Human infection result from eating raw or underlooked parasitized fresh water fishes. In human the infected parasite resides in the duodenum and ascends the bile ducts and canaliculi where they mature and may cause biliary epithelial hyperplasia and fibrosis. Similarities between the histopathological response in infected humans and experimental animals have seen documented including the development of cholangiocarcinoma in dogs and cats experimentally infected with *Clonorchis*[16]. This and other observational studies are in keeping with the experimental evidences pointing to infection as a promoter of carcinogenesis[16,17].

In the Far East, nitrosamines are commonly found in traditional Chinese foods such as salted fish, dried shrimp and sausage. Metabolites of nitroso compound have been identified in the body fluids of men infected with *O. Viverrini*. Pancreatic duct infected with *C. sinensis* is associated with squamous metaplasia and adenocarcinoma[17]

**MALARIA**
The geographic distribution of Burkitt lymphoma in the classic malaria belt initially suggested the possible role of the arthropod vector in oncogenesis[17,19]. This fits the notion that the risk of lymphoma declines with increasing westernization and effective malaria eradication[22, 23]. This possibility has been argued to be unlikely, because extensive malaria prophylaxis carried out in Madagascar Republic and some West African countries still had endemic Burkitt lymphoma[24].

However, more significantly there has been a linked between endemic Burkitt lymphoma and Epstein-Barr virus (EBV)[20]. During malaria infection, there is always a vigorous cellular and serological responses; this is believed to stimulate the immune system among the population with malaria endemicity. The hyperimmune status in EBV-infected African patient tends to lead to

the development of a neoplasm rather than a self-limited infectious mononucleosis[26,28]. This view finds support in the observation that each one of the erythrocytic, exoerythrocytic and sexual forms of the parasite is structurally differentiated and probably contain many biologically active antigenic components[19]. It has also been observed that in malaria endemic belt, the peak age incidence of Burkitt lymphoma correspond to peak age, incidence of severe falciparum malaria [23].

One explanation of this observation is that the malaria patient harbours multitudes of parasite-derived antigens, and then the patient becomes a host susceptible to endemic Burkitt lymphoma. It is also observed that malaria patients produce so many antibodies that are non-specific and do not recognize or respond to lymphoid cells habouring Burkitt lymphoma[26]. It is also seen that acute malaria increases B cells proliferation, and also impairs EBV-specific T cells response[24]. The clinical manifestations probably are promoted by other environment factors [27,28].

In the carcinogenesis of Burkitt lymphoma, malaria may be considered as an initiator and EBV as a promoter or vice versa. Neither of the hypothesis accounts for the fact that invitro injection of B-cells with EBV and stimulation with malaria antigen has not produced a cell that carries the signature characteristic of chromosome translocation found in both sporadic and endemic Burkitt lymphoma [28,29].

Over expression of C-MYC appear to be central to the pathogenesis of Burkitt and atypical Burkitt lymphoma. Although C-MYC translocation occurs in all case of Burkitt lymphoma, differences are seen in translocation patterns in endemic and sporadic Burkitt lymphoma. Typically, sporadic Burkitt lymphoma has translocation involving sequences within MYC on chromosome 8 and sequence within or near the immunoglobulin heavy chain S-region on chromosome 14. In contrast, endemic Burkitt lymphoma tends to be characterized by a translocation involving sequences on chromosome 8 of further upstream from MYC, and sequence within or near JH region on chromosome 14[28,29,30]. It is likely that other environmental, genetic or nutritional factors may be involved in the tumourigenesis.

## REFERENCES


1. **Mandong BM.** Carcinoma of urinary bladder in Jos, Nig, *Med. Pract*. 1997; **33**: 33-36.
2. **Mandong BM.** Malignant diseases in Jos University Teaching Hospital, Nigeria. Nig Med Pract. 1999; 37(4): 55-58
3. **Mandong BM, Andteyi EA, Ujah IO**: Restrospective study of squamous cell carcinoma of the urinary bladder in North central Nigeria. *Niger Med. J*. 2000 (3); **1**:10-12
4. **Mustacch P.** Parasites. In: Holland J. F, Frei E. III, Bast RC et al, (eds) Cancer Medicine, 6th Ed. Helmito BC Decker Inc 2003; p. 359-365.
5. **Cheever AW.** Schistosomiasis and Neoplasia. *J Natl Cancer Inst*. 1978; **61**; 13-17.
6. **Gentile JM.** Schistosome related cancers; a possible role for genotoxins. *Env. Mutagen* 1985; **7**:776-778.
7. **Bedwani R, El-Khwisky F, La vecchia C.** et al. Descriptive Epidemiology of bladder cancer in Egypt. *Int. J Cancer* 1993; **55**: 351-354.
8. **Tricker AR, Mostafa HH,** Spiegelhalder P, Preussma P. Urinary Nitrites and Nitroso compounds in bladder cancer patient with schistosomiasis. IARC Sci Pub. 1991; 105: 178-180.
9. **Abdel Mohsen M,A, Hassan A A M, El-Sewedysm** et al, biomonitoring of Ni-Nitroso compounds, Nitrites and Nitrate in the urine of Egyptians bladder cancer patients with or without schistosomiasis haematobium infection. *Int. J. Cancer* 1999; **82**:789-790.
10. **Warren W, Biggs P J, Ek-Bas M.** et al. Mutation in the P53 gene in Schistosomal bladder cancer: a study of 92 tumours from Egyptian patients and a comparison between mutational spectra from schistosomal and non-schistosomal urothelial tumours. *Carcinogenesis* 1995; **16**: 1181 -1184.
11. **Badawi AA.** Molecular and genetic events in schistosomiasis associated human cancer: Role of oncogene and tumour suppressor gene. *Cancer Let*t 1996; **105**: 123 125.
12. **Habuchi T, Takahashi R, Yamadatt,** et al. Influence of cigarette smoking and schistosomiasis on P53 gene mutation in urothelial cancer. *Cancer Res* 1993; **53**: 3795-3796.
13. **Chen M C, Chuang CY, Chang P Y, Hu TC.** Evolution of colorectal cancer in Schistosomiasis. *Cancer* 1993; **20**:13-18.
14. **Yu Z, Su DL.** Schistosoma japonicum and colorectal cancer: an epidemiological study in the Peoples Republic of China. *Int J Cancer*. 1984; **34**:315-318.
15. **Schwartz D A:** Cholangio-carcinoma associated with liver fluke infection, a preventable source of morbidity in Asian Immigrants; *Am J. Gastroenterol* 1986; **81**: 76-80.
16. **Haswell Elkins MR, Satame, S. Tsuda M,** et al. Liver fluke infection and cholangio-carcinoma model of endogeneous nitric oxide and extra gastric Nitrosation in human carcinogenesis. *Mutat Res*. 1994; **304**:241-252.
17. **Colquhum BPD.** Adenocarcinoma of the pancreas associated with C. sinensis infection. CMAJ 1987; 136:153-156.
18. **Sadoff L.** Aetiology of Burkitt's lymphoma. *Lancet* 1973; **2**.1262-1266.

19. **Sadoff L.** Aetiology Antimalaria Drugs and Burkitts Lymphoma. *Lancet* 1973; **2**:1262-1264.
20. **Facer CA, Playfair JHL.** Malaria, Epstein Barr virus and the genesis of the lymphoma: *Adv Cancer Res*. 1989; **53**: 33-40.
21. **O'Conor GT.** Persistent immunologic stimulation as a factor in oncogenesis with special reference to Burkitts tumour. *Am J Med*. 1970; **48**:279-281.
22. **Kreger G, O'Conor GT.** Epidemiologic and immunologic considerations on the pathogenesis of Burkitt's tumour. Recent Result; *Cancer Res*. 1972; **32**:211-216.
23. **Facer CA, Playfiar JHL.** Malaria Epstein Barr virus and the genesis of the lymphoma. *Adv. Caner Res*. 1989; **53**:33-39.
24. **O'Connor GT.** Persistant Immunoglobulin's stimulation as a factor in oncogenesis with special reference to Burkitt tumor. *Am J Med*. 1970; **1**:742 -750.
25. **Warren AE,** Burkitt's Lymphoma and disordered Immunoglobulins response. *Lancet* 1974; **1**:147-750.
26 **Kregar G, O'Connor GT.** Epidemiologic and immunologic consideration on the pathogenesis of Burkitt tumor. Recent Results. *Cancer Res*. 1972; **32**:211-218.
27 **Magrath I.** The pathogenesis of Burkitt lymphoma. *Adv. Cancer Res* 1990; **274**:756-760.
28. **De-The G, Geser A, Day NE** et al. Epdemiological evidence of casual relationship between Epstein Barr virus and Burkitt lymphoma from Uganda Prospective study. *Br J Cancer* 1993; **68**:1232-1239.
29. **Morrow RH.** Epidemiological evidence for the role of faciparum malaria. In Lenoir G, O'Connor G. Olweny C, (editors). Burkitts lymphoma: a human cancer model. Lyon: IARC. 1985; 54:387-390.
30. **Bishop PC, Rao K, Wilson WH.** Burkitts lymphoma: Molecular pathogenesis and treatment. *Cancer Invest.* 200; **18**:574-582.