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Review Article

ASSOCIATION OF PARASITIC INFECTIONS AND CANCERS

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Abstract

Recent advances in the fields of molecular biology, epidemiology and infectious diseases have led to significant revelations to clarify the relationship between cancer and infective agents. This article reviews the relationship between parasitic infections and carcinogenesis and the possible mechanisms involved. Few parasites, e.g., *Schistosoma haematobium* and O*pisthorchis viverrini* have been found to be strongly associated with bladder cancer and cholangiocarcinoma respectively. The evidence for the association of several other parasites and cancers has also been postulated.

Key words: *Cancer, Cysticercosis. Liver flukes, Parasites, Schistosomiasis, Trichomoniasis, Toxoplasmosis*

Recent advances in the fields of molecular biology and epidemiology have led to significant revelations to clarify relationship between infectious agents and cancer and have given valuable insights into the molecular basis of carcinogenesis. Rous in 1911 is credited as being the first person to show that cancer can have an infectious origin, when he demonstraed cell free filtrate from chicken sarcoma to cause cancer in a second animal. Between 1931 and 1972, 26 mammalian oncoviruses were discovered. In response to these discoveries, the US virus cancer programme was initiated in 1960s marking the start of the era during which the infectious origin of cancer became a dominant hypothesis.[1] It is estimated that over 15% malignancies worldwide can be attributed to infections; the figures are higher in developing countries to the extent of 22% compared to about 7% in developing countries. The incidence of malignancy due to an infectious cause is about 1.2 million cases per year.[2] This also implies that at least some of the cancers are preventable and should be a thrust area for research.

Infectious agents including parasites that have an oncogenic potential are often highly prevalent within the host population. They persist in the host and removal of the parasite may result in reversal of tumor development. However, high prevalence of parasitic infection in the general population, their persistence in the host, co-infections with other microbes and other interacting factors like nutritional status etc. make the establishment of relationship difficult.[1]

Infections in general can initiate or promote carcinogenesis by any of the 3 main mechanisms:

1) Chronic inflammation due to prolonged persistence of infectious agent in the host: Phagocytes at the inflammatory site release reactive oxygen radicals and reactive nitrogen radicals having the potential to damage DNA, proteins and cell membranes, alter enzyme activities and gene expression which in turn can induce carcinogenesis. Moreover, chronic inflammation leads to repeated cycles of cell damage and compensatory cell proliferation, thus promoting neoplasia.[3]

2) Insertion of active oncogene in the host genomes: This usually occurs in oncogenic viruses. The oncogenes may inhibit tumour suppressor genes or directly stimulate mitosis.[4]

3) Reduced immunosurveillance as a result of immunosuppression: In all the forms of immunodeficiency, the relative risk of developing tumors, especially those in which viruses are known to play a role are greatly increased. The course of cancer in immunocompromised host is generally aggressive although other risk factors remain unchanged.[4]

This article reviews the parasitic diseases associated with neoplasms

Schistosomiasis

It is the second most common parasitic infection of humans after malaria. Approximately 200 million people are infected globally in 76 countries and about 600 million are exposed to infection in tropical and subtropical regions of Africa, Asia, South America and the Caribbean. Schistosomiasis is caused by the trematode (blood flukes) of genus *Schistosoma*. The parasites pass their life cycle in a mammalian definitive host and an invertebrate intermediate host, the fresh water snails. *Schistosoma* larvae are released from the snails into fresh water as free-living cercariae, which penetrate the skin of the mammalian host. Here the parasites develop into schistosomulae which migrate through blood stream to liver where they mature into adult and eventually

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release eggs into blood stream which either lodge into tissues and incite inflammatory reaction or are released in the urine or faeces. The eggs hatch in water to form miracidia which invade snails.[5]

Mainly five species infect humans namely *S. haematobium, S. mansoni, S. japonicum, S. intercalatum* and *S. mekongi.* Most human infections are due to *S. haematobium* and *S. mansoni.* The adult worms of *S. japonicum* and *S. mansoni* reside in the inferior mesenteric vein although *S. japonicum* also resides in the superior mesenteric vein. *S. haematobium* inhabits the terminal venules in the wall of the bladder, the genitourinary system and the pelvic plexus within the distribution of the inferior vena cava. However, it can also exist in perirectal venules excreting the eggs in the stool. At oviposition, the eggs are immature but miracidial maturation takes place in a few days. Soluble egg antigens (SEA) originating from the secretary glands of miracidia enclosed within eggs diffuse out through submicroscopic pores in the eggshell and induce an acute host hypersensitivity response. The immunopathology is due to granuloma formation around the eggs deposited in the tissues and is a manifestation of delayed hypersensitivity reaction. This leads to pylephlebitis, peripylephlebitis, portal hypertension, splenomegaly, oesophageal varices, haematemesis and death. One particularly dreaded complication is cancer.[5]

The international agency for research on cancer (IARC) considers *S. haematobium* infection a definitive cause of urinary bladder cancer with an associated 5-fold risk.[2] This conclusion is based on ecological studies reporting strong positive correlation, case reports and several case control studies.[6] Bladder cancer associated with *S. haematobium* is histologically and pathologically distinct from non *S. haematobium* associated bladder cancer occurring in North America and Europe, the former being a squamous cell carcinoma, with an earlier age of onset and generally sparing the trigone of bladder while the latter is of transitional cell type occurring in the older age group.[5,6] Several mechanisms have been suggested to explain the role of *S. haematobium* in bladder cancer:

Fibrosis induced by schistosome eggs may induce proliferation, hyperplasia and metaplasia, all of which are possible precancerous changes.[7]

Chronic urinary bacterial infection and production of nitrosamines from their precursors in urine, that are well known bladder carcinogens.[8]

Urinary stasis allowing concentration of endogenous carcinogens leading to their absorption from urine and exposure of the bladder epithelium.[9,10]

Raised urinary beta-glucuronidase levels originating from miracidia and adult schistosomes liberating carcinogenic amines in urine.[11]

The evidence supporting role of *S. japonicum* in cancer occurrence is weaker, although it has been associated with both liver and colorectal cancer.[12] Thus, presently *S. japonicum* can be considered a possible carcinogen for humans. Epidemiological and clinical studies in China and Japan support a probable role of *S. japonicum* infection as one of the risk factors in hepatocellular carcinoma (HCC) formation. Additional risk factors include viral infection with Hepatitis B (HBV) and Hepatitis C viruses (HCV) and alcohol abuse.[12,13] Experimental studies have shown that liver cancer appears early and in larger numbers in animals experimentally infected with *S. japonicum* and given a known carcinogen.[12] Case control studies in China and Phillipines and epidemiological cross-sectional surveys in China have suggested both positive and negative associations. One case control study in China showed a strong association between *S. japonicum* infection and rectal cancer but no association between *S. japonicum* infection and colonic cancer.[14]

The link between *S. mansoni* and HCC appears to be an indirect one. Patients with *S. mansoni* have higher rates of HBV and HCV infection compared to noninfected controls.[15,16] The higher exposure of schistosomiasis patients to HBV and HCV could be explained partly, by transmission of these viruses during blood transfusion and parenteral therapy for schistosomiasis via contaminated blood, needles and syringes.[17,18] Furthermore, studies have shown that the cell mediated response is depressed in active intestinal schistosomiasis and this immunosuppression increases with advancement of the disease and development of hepatosplenomegaly.[19,20] These patients tend to retain HBV and HCV for longer periods and attain carrier state with a higher risk of developing complications including HCC.[16,21,22] *Schistosoma* infections affect the immune response in two ways that may prolong the carrier state of the virus. Anti-idiotype antibodies produced in patients with chronic schistosomiasis can downregulate specific immune responses and suppress nonspecific immune responses.[23] In addition, various studies in mice and humans have shown that *S. mansoni* egg antigens can modify subpopulations of thymus helper cells. Th2 activity and the cytokines involved with eosinophilia and IgE secretion are stimulated while Th1 activity and the cytokines, IL2 and interferon gamma, as well as CD8+ cytotoxic T cells are downregulated in BALB/C mice infected with *S. mansoni*.[24]

Opisthorchis and Chlonorchis Infections

O. viverrini, O. felineus and *C. sinensis* are flatworms inhabiting the human liver. They remain important public health problem in many endemic areas where they infect at least 20 million people. In addition to their association with hepatobiliary disease, they are major aetiological agents of bile duct cancer. This is a leading cause of death in northeast Thailand.[25] The adult hermaphrodite parasites live in the smaller intrahepatic bile ducts of their final hosts, which include humans, dogs, cats and other wild and domestic animals. Eggs are laid in the biliary system and are excreted

in the faeces, which are ingested by the first intermediate hosts, the *Bithynia* snails. The eggs hatch inside the snails and eventually mature leaving the snail in the form of freely swimming cercariae, which in turn penetrate the fish, the second intermediate host where they develop into metacercariae. Ingesting raw, pickled or undercooked fish infects humans. The metacercariae excyst in the duodenum and jejunum and migrate through the ampulla of vater into the bile duct where they mature into adult flukes that can live there for up to 30 years. The most chronically infected individuals have few specific signs or symptoms except an increased frequency of palpable liver. Symptomatic cases generally experience pain in the right upper quadrant of the abdomen, diarrhoea, loss of appetite, indigestion etc. The most important complication of liver fluke infection is an enhanced susceptibility to cholangiocarcinoma.[25] After evaluating epidemiological studies, case series and case control studies, the IARC concluded that *O. viverrini* is a definite human carcinogen whereas evidence for the carcinogenic effect of *O. felineus* and *C. sinensis* is more limited.[26] Many cases of liver cancer arising in patients with *O. viverrini* infection have been reported from Thailand. In most regions of the world, cholangiocarcinoma is a very rare tumour. In areas where *O. viverrini* is endemic, however, the numbers of cases of cholangiocarcinoma generally outnumber those of hepatocellular carcinoma.

A number of cross-sectional or case-control studies on the association between *O. viverrini* infection and cancer of the liver have been reported from Thailand. In the first large case study, an unusually high incidence of cholangiocarcinoma was obsvered in both the autopsy and biopsy materials taken from the patients with of *O. viverrini* infection.[27] The ratio between hepatocellular carcinoma and cholangiocarcinoma in autopsies without opisthorchiasis was 8:1, whereas the ratio was reversed among those with liver fluke infection. Similarly the ratio of these two malignancies in biopsies was 5:1 in non-infected patients and 1:2 in the presence of the fluke.[27] Similar results have been confirmed by other authors who showed that the incidence of cholangiocarcinoma was almost twice that of hepatocellular carcinoma in endemic areas of *O. viverrini* in the north-east of the country, and the incidence in males was 2.4 times that in females.[28] In another case control study, the *O. viverrini* infection increased the risk of cholangiocarcinoma fivefold.[29]

The incidence of liver cancer was observed to be correlated with the prevalence of infection with *O. felineus* across four areas in the T'umen' region of north-west Siberia. Cases of both cholangiocarcinoma and hepatocellular carcinoma have been reported in people infected with *O. felineus.*[26]

There is ample evidence that *Clonorchis sinensis* is also associated with cholangiocarcinoma. Cases of cancer of the liver in association with infection with *C. sinensis* have been reported from China, Hong Kong, the Republic of Korea and Japan and in immigrants to North America from China and Laos. In Pusan, an area with extremely high prevalence of *C. sinensis*, the fluke increased the risk of cholangiocarcinoma sixfold.[30] Another case control study in the same area showed that *C. sinensis* in the stool was significantly associated with cholangiocarcinoma with estimated relative risk of 2.7.[31] Cases of cholangiocarcinoma, associated with *C. sinensis*, have also been reported among Asian immigrants to the USA.[32,33]

The following possible mechanisms of carcinogenesis due to liver fluke infections have been postulated:

1. Hyperplasia of bile duct epithelium and carcinogen exposure: Chronic irritation and chronic inflammation caused by the fluke results in hyperplasia and adenomatous changes of bile duct epithelium. These hyperplastic cells are vulnerable to carcinogen because the agent can easily induce DNA damage during active cell proliferation.[34]

2. Increased formation of endogenous carcinogen: Endogenous nitrosation caused by liverfluke infestation has been studied in both humans and animals. It is likely that N-nitroso compounds are formed in the area of chronic inflammation around the bile ducts as the result of local generation of nitric oxide by inflammatory cells. Therefore, bile duct epithelial cells are exposed continuously to high concentrations of nitroso compounds leading to neoplastic transformation.[35]

3. Activation of drug metabolizing enzymes: In male hamsters infected by *O. viverrini*, activities of hepatic cytochrome p-450 isoenzyme have been shown to be higher than those of controls especially in hepatocytes in the area of inflammation. N-nitrosodimethylamine, one of the products of endogenous nitrosation formed in the tissue, is significantly metabolized by cytochrome P-450. The product of this metabolism is a DNA methylating agent that can result in DNA damage, particularly in proliferating bile duct epithelial cells. There was a significant reduction in the levels of these enzymes after eradication of flukes by praziquintal treatment.[36]

4. Increased nitric oxide production: In areas of chronic inflammation caused by the liver fluke, macrophages and other cell types (e.g mast cells, eosinophils), activated by parasite specific T cells and cytokines, synthesize nitric oxide (NO) from L- arginine**.** NO is not only cytotoxic but may also be genotoxic leading to DNA damage.[35,37]

Thus, it is probable that all the above four mechanisms may act in concert during the development of cholangiocarcinoma. However, very low incidence of cholangiocarcinoma in countries showing a high prevalence of *Opisthorchis* and *Clonorchis* indicate that cofactors are important for carcinogenesis. Animal studies show that in absence of carcinogens, cholangiocarcinoma is unlikely to develop in *Opisthorchis* and C*lonorchis* infection. So these

liver flukes are, for the most part, promoters and not initiators of cholangiocarcinoma.

Trichomoniasis

Trichomonas vaginalis is a pathogenic protozoan, which resides in the lower female genitourinary tract. Infection may or may not be symptomatic. It is sexually transmitted and occurs worldwide in both urban and rural populations. In sexually transmitted disease clinics, overall infection rates varying from 7 to 32% have been recorded.[38] Highest prevalence figures are in groups with a high level of sexual activity. The organism is frequently coexistent with other infections like candidiasis, bacterial vaginosis, gonorrhoea or HIV infection. The classical clinical presentation is that of vulvovaginitis with a greenish yellow frothy discharge. Some may have vulval irritation or dyspareunia. In men, majority of infections are asymptomatic although few may present as nongonococcal urethritis.[38]

Many researchers have studied the association between *T. vaginalis* infection and cervical neoplasia.[39-44] Most studies have shown an association between *T. vaginalis* and risk of cervical neoplasm though a cause and effect relationship has not been proven. Few studies however have shown no association between the two.[42] The proof of association comes from either serological or histopathological studies. Antibodies to *T. vaginalis* have been detected in 18 to 43% of invasive cervical neoplasia compared with only 5% in the control groups and the risk ratio was found to be 3.42.[39] The increase in antibody titre was especially evident in the 40-49 year age group and in patients with squamous cell carcinoma especially grade II and III.[39,40] In an analysis of available data from studies on association between *T. vaginalis* infection and cervical neoplasia, a total of 24 studies (2 cohort and 22 case control) were included.[45] The combined summary relative risk for the two cohort studies was 1.93 indicating an approximate doubling of the risk of cervical neoplasia in presence of *T. vaginalis* infection. The attributable risks among exposed subjects and source population were 47.4% and 2.15% respectively. Results of the 22 retrospective studies are much less consistent, however, most of these demonstrated a significant positive association.[45]

Toxoplasmosis

There are a few reports in the literature about the relationship between *Toxoplasma gondii* infection and tumours including primary ocular tumours, meningioma, leukemia and lymphoma.[46] Zhang *et al* described two cases of pituitary adenoma associated with *T. gondii*.[47] The toxoplasma cysts were found among the tumour cells and were verified using *T. gondii* specific antibody by immunohistochemistry.[47] In another study investigated in two parts,[48] one based in Adelaide, South Australia, and the other based in Melbourne, Victoria, all tumors were verified histologically and IgG antibodies to *T .gondii* were measured by ELISA. Both the studies suggest that the possession of antibody to *T. gondii* is unlikely to be a risk factor for glioma. The Adelide study provides some evidence that seropositivity may be associated with meningioma.[48] It has been demonstrated in experimental studies that exogenous prolactin has antiparasitic effects.[49] Thus, the postulate has been put forward that overstimulation of pituitary gland to fight the parasitic infection, may lead to adenoma formation. However, no further research regarding the role of *Toxoplasma* in tumorigenesis has been reported.

Neurocysticercosis

Neurocysticercosis (NCC) caused by the cysticerci of helminth *Taenia solium* has recently been associated with local malignant tumors particularly glioblastoma multiformae and even neoplasia originating outside the nervous system e.g., the malignant haematological diseases. One study found NCC to be a risk factor for development of cerebral glioma.[50] The odds ratio was 7.63(95% confidence interval 2.03-31.09).[50] The possible mechanisms may be:

a) Chronic inflammation leading to release of nitric oxide in brain which is a potential carcinogen.[51]

b) The parasite induced modulation of host immune response leading to inhibition of tumour suppressor surveillance mechanisms.[51]

c) The transfer of genetic material from parasite to host causing DNA damage thus predisposing to carcinogenesis.[41]

In an epidemiological study, the NCC was found to be more frequent in cases with malignant haematological diseases than in controls.[52] The odds ratio for this association was 3.5 (95% confidence interval 1.2-9.8).[52] It has been shown that the chromosomal aberrations induced in peripheral lymphocytes during NCC could be an important factor.[53] Further research is needed to confirm the potential role of cysticercosis in carcinogenesis.

In summary, whereas some parasitic infections like *O. viverrini* and *S. haematobium* are very strongly associated with cancers and are important predisposing factor for specific cancers, some other parasites may have probable role in development of certain cancers. Early diagnosis, prompt treatment and prevention of such infections may help in significant reduction in occurrence of these cancerous conditions.

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