2. Studies of Cancer in Humans

Concern about a causal relationship between infection with schistosomes and cancer is based on observations of patients who have been exposed to *S. haematobium*, *S. japonicum* and *S. mansoni*.

2.1 Descriptive studies

2.1.1 *Schistosoma haematobium*

The proportion of all cancers represented by urinary bladder cancer varies greatly within Africa and the Middle East, and the ratio of male to female frequency of occurrence is nearly as variable (Parkin, 1986). In Egypt, the proportion of bladder cancers among all cancers in men is twice that in Zambia, four times that in Zimbabwe and 10 times that in Algeria. Very few formal assessments of the correlation between bladder cancer incidence and the prevalence of *S. haematobium* have been done, but there are many informal descriptions of geographical correspondence between the areas affected by the two diseases.

Most of the early clinical descriptions of urinary bladder cancer in connection with evidence of schistosomiasis come from the Nile Delta, where there are few unexposed populations and no population-based incidence data (see section 2.2.1); however, in countries with less universal exposure, observations have been made on the geographical relationship between exposure to *S. haematobium* and bladder cancer occurrence. The common geographical pattern of occurrence of *S. haematobium* and bladder cancer has been noted by investigators in almost all endemic African countries (Table 2).

In addition to the link between the risk of a subpopulation for a haematobium schistosomiasis and the risk of the same population for urinary bladder cancer, a slightly more direct link has been noted; the proportion of bladder cancers that are squamous histologically in the population of a country is related to the proportion of cancerous bladder specimens from that population which contain evidence of past schistosomal infection in the form of eggs or egg remnants (Lucas, 1982a). This has been noted even within countries; in Iraq, for example, 36.1% of bladder cancer cases from the north are squamous-cell tumours and 4.9% have evidence of *S. haematobium*, whereas in the south, where *S. haematobium* is more prevalent, 54.8% are of the squamous variety and 32.2% have evidence of *S. haematobium*; those from the central part of the country show intermediary rates of 48.5% and 20.7%, respectively (Al-Fouadi & Parkin, 1984).

The two diseases have other characteristics in common. In a description of the pattern of urinary bladder cancer by occupation in the Nile Delta, 99% of the bladder cancers occurring in high-risk male agricultural workers (*fellahin*) were found to be associated with histological evidence of *S. haematobium* infection, whereas only 52% of the cases occurring in men with lower-risk occupations showed such evidence (Makhyoun *et al.*, 1971).

Table 2. Descriptive studies of infection with *Schistosoma haematobium* and urinary bladder cancer

Reference	Location	Outcome index	Exposure index	Geographical correlations	Secular or occupational correlations	Correlated sex ratios or age distributions
Talib (1970)[a]	Iraq, referral hospital	Proportional frequencies	Common knowledge	More patients from south and centre, where *S. haematobium* is endemic	–	–
Anjarwalla (1971)	Kenya, referral pathology service	Proportional frequencies	Frequency of schistosomiasis diagnoses and school surveys	Patients from coastal area, where schistomiasis is common	–	–
Makhyoun *et al.* (1971)[a]	Egypt, Nile Delta University hospital	Proportional frequencies	Common knowledge	–	Cases in male *fellahin*: 99% histologically *S. haematobium* egg-positive Cases in men in other occupations: 52% positive	Exceptionally higher sex ratio for bilharzial cases (11.8:1) than for non-bilharzial (4.8:1), low-risk British (4.1:1) cases or high-risk Mozambican cases with exposure during field work (0.9:1)
Anthony (1974)	Uganda, referral hospital	Proportional frequencies	Frequency of schistosomiasis diagnoses	Bladder cancer, including squamous-cell cancers, unrelated to small foci of schistosomiasis	–	–
Bowry (1975)[a]	Kenya, referral pathology service	Proportional frequencies	Frequency of schistosomiasis diagnoses and school surveys	Cancer foci on coast and near Lake Victoria, both known foci of schistosomiasis	–	–
Malik *et al.* (1975)[a]	Sudan, referral hospital	Proportional frequencies	Ministry of Health records of 'highest endemicity'	Correspondence between frequency of bladder cancer and endemicity by province	–	–
Keen & Fripp (1980)[a]	South Africa (Transvaal)	Frequencies identified in regional surveys	None explicit	–	–	Wide variations in sex ratio (from 2:1 to 1:2) according to region and tribe
Lucas (1982)[a]	Africa	Proportional frequencies	Histological identification of *S. haematobium* eggs in bladder specimens	Geographical distribution of percentage of histologically *S. haematobium* egg-positive tumours correlated directly with percentage of all bladder cancers that are squamous-cell and inversely with the percentage that are transitional-cell tumours		

Table 2 (contd)

Reference	Location	Outcome index	Exposure index	Geographical correlations	Secular or occupational correlations	Correlated sex ratios or age distributions
Hanash (1984)	Saudi Arabia, referral hospital	Proportional frequencies	Known distribution of *S. haematobium* endemicity	Bladder cancer cases commonly come from endemic communities	–	–
Al-Fouadi & Parkin (1984)[a]	Iraq, urban hospitals	Registered cases	'Known distribution of *S. haematobium* endemicity'	Percentage of tumours that are squamous-cell and percentage of tumours that contain histologically identifiable *S. haematobium* eggs closely related to southern latitude [proximity to the river delta]	–	–
Kitinya *et al.* (1986)[a]	United Republic of Tanzania, referral hospital	Proportional frequencies	Known distribution of snail vectors in relation to altitude	Low proportion of squamous-cell tumours and low prevalence of *S. haematobium* at high elevations near Mt Kilimanjaro	–	–
Tawfik (1988)[a]	Egypt, referral hospital	Proportional frequencies	Histological identification of *S. haematobium* eggs in bladder specimens; records of control programme	–	High bladder cancer proportional frequency despite 20 years of successful control efforts (prevalence reduced from 60 to 10% in one province)	High sex ratio correlated with documented intensity of infection. As period of successful control efforts lengthens, mean age of bladder cancer increases.
Thomas *et al.* (1990)	Zimbabwe, referral hospital	Proportional frequencies	National prevalence surveys among schoolchildren	Estimated bladder cancer incidence correlated with prevalence of *S. haematobium* infection ($r = 0.87$; $p < 0.01$). Ratio of squamous-cell to transitional-cell tumours linked to *S. haematobium* prevalence: 12:1 where prevalence was 67%, 2:1 where prevalence was 17%	–	Sex ratio for squamous-cell tumours, 1.0; for transitional-cell tumours, 2.9:1.

[a]Correlation not formally tested

Whereas in the Nile Delta, where men do most of the agricultural work, the ratio of male to female cases of urinary bladder cancer with histological evidence of past infection may be as high as 12:1 (Makhyoun *et al.*, 1971), the sex ratio among those without such evidence approximates the 4:1 ratio seen in the United Kingdom (Prates & Gillman, 1959). In contrast, in Mozambique (Prates, 1963) and adjacent regions of the Transvaal in South Africa (Keen & Fripp, 1980), where women do most of the agricultural labour and are therefore more commonly infected, the sex ratios are reversed to 1:1.1 or even 1:2, even though ratios of 2:1 prevail among cases referred from nearby areas. The sex ratio of bladder cancer cases has also been linked to the histologically measured intensity of infection in tumour specimens, and ranged from 8.7:1 in heavily infected people, to 4:1 in those who are lightly infected, to 2:1 in those without eggs in Egypt (Tawfik, 1988).

In a community in Angola, where both males and females work in agriculture, the minimal age of infection with *S. haematobium* was 11 years. The mean age of patients with urinary bladder carcinomas associated with schstosomiasis was 44 years. The sex ratio was 1.6:1 for bladder carcinoma associated with schistosomiasis and 3.2:1 for bladder carcinoma not associated with schistosomal disease ($p \sim 0.05$) (da Silva Lopes, 1984).

It should be noted, however, that in Uganda, squamous-cell carcinomas of the urinary bladder are commoner than in Europe or North America in the absence of any relationship to known *S. haematobium* prevalence (Anthony, 1974).

Because of the lack of population-based cancer registration, the secular trends in incidence of squamous- or transitional-cell carcinomas of the urinary bladder have not been formally evaluated. In an area of the Nile Delta where the prevalence of *S. haematobium* infection was brought from a level of 60% in 1968 to 10% in 1988, no impact upon the rate of bladder cancer was clinically evident at the end of that period, although the mean age at diagnosis had increased (Tawfik, 1988).

2.1.2 *Schistosoma mansoni*

No description has appeared of the geographical occurrence of cancer in relation to the prevalence of *S. mansoni* infection. In relation to liver cancer, one observer pointed out that the pattern of occurrence in Africa and South America does not correspond to that which would be expected on the basis of a strong association with *S. haematobium* (Edington, 1979). The absence of any geographical relationship between colorectal cancer and colorectal schistosomiasis in Africa is even clearer. Despite wide variations in the geographical distribution of *S. mansoni*, colorectal cancer occurs in Africa with remarkable uniformity, insofar as the proportion of cases among all cancers provides pertinent information (Parkin, 1986). Moreover, reports from multiple centres in north, east, south and west Africa all indicate that evidence of schistosomal infection in colorectal tumour specimens is no commoner than would have been expected on the basis of the known prevalence of infection (Murray, 1967).

2.1.3 *Schistosoma japonicum*

The geographical co-occurrence of *S. japonicum* and cancer has been assessed formally (Table 3). Unfortunately, interpretation of the geographical patterns of occurrence of liver and colorectal cancers in Asia is difficult, because of known variations in the distribution of other causes of the same neoplasms, including hepatitis viral infection, dietary nutrients and carcinogenic dietary contaminants such as aflatoxins. In particular, a large correlation study from China assessed the association between mortality from schistosomiasis and from colorectal, liver, oesophageal and gastric cancers (Liu *et al.*, 1983). Correlations were calculated at two geographical levels: in 24 provinces of varying endemicity and in 10–98 counties within six provinces of high endemicity. [The Working Group noted that, in addition to the problems common to the interpretation of all correlation studies (see Preamble, p. 22), interpretation of studies correlating mortality from cancer and from schistosomiasis are complicated by the low diagnostic specificity of the latter cause of death; however, such misclassification of cause of death would probably lead to an underestimated correlation coefficient.]

(*a*) *Liver cancer*

In the study of Liu *et al.* (1983) in areas of high endemicity in China, significant correlations were found for both men and women in one province, while in four other provinces, the correlations were significantly positive only for women. No correlation was found in an analysis of 24 provinces, or in the seven endemic counties in Jiangsu Province (Guo *et al.*, 1984).

Within areas of Yamanashi Prefecture, Japan, classified on the basis of prevalence rates of schistosomiasis in 1958–62 [survey method not specified], the standardized mortality ratios for liver cancer on the basis of mortality in Japan were found to be significantly higher (at the 95% level) than those predicted in non-endemic areas and especially in aggregates of local endemic areas (Inaba *et al.*, 1977). Positive correlations were found between these prevalence rates and liver cancer rates in individual local areas in 1968–72, which were significant at the 95% level only for men (Table 3). The correlations for men increased in the period 1970–75, and while the correlation for women in that period became positive it remained compatible with chance. No adjustment was made for possible covariation with prevalence of hepatitis viral infection.

In a separate analysis analogous to that for liver cancer, Inaba (1982) assessed the frequency of mortality from other gastrointestinal malignancies in endemic areas by examining standardized mortality ratios in relation to those for Japan as a whole. No excess of cancer of the oesophagus, stomach, colon or rectum was noted for people of either sex, although the ratios of cancers of the bile duct and the pancreas in men were slightly but significantly elevated in endemic areas.

(*b*) *Cancers of the oesophagus and stomach*

In the study of Liu *et al.* (1983), significantly positive correlations were found for both stomach and oesophageal cancer for men and women in one province (Jiangxi), while the results for other provinces were inconsistent. No correlation was suggested in the analysis of 24 provinces with respect to stomach cancer. In another analysis (Guo *et al.*, 1984), no

Table 3. Descriptive studies of infection with *Schistosoma japonicum* and cancer

Reference	Population observed	Outcome index	Exposure index	Geographical correlations
Inaba *et al.* (1977)	Japan, Yamanashi Prefecture, localities	HCC mortality rate, 1968–72, 1970–75	Prevalence of schistosomiasis, both sexes, 1958–62	1968–72, males: 0.303*; females: -0.067 1970–75, males: 0.463*; females: 0.236
	Japan, Yamanashi Prefecture, endemic *versus* non-endemic areas	HCC mortality rate, 1970–75	Prevalence of schistosomiasis, both sexes, 1958–62	SMR, endemic males, 156 ± 21 females, 148 ± 26
				SMR, non-endemic males, 127 ± 17 females, 128 ± 21
Liu *et al.* (1983)	China, 24 provinces	Stomach cancer mortality rate	Schistosomiasis mortality rate	Not correlated
		Liver cancer mortality rate	Schistosomiasis mortality rate	Not correlated
		Colorectal cancer mortality rate	Schistosomiasis mortality rate	Males, $r = 0.695, p < 0.001$; females, $r = 0.625, p < 0.005$
	China, 10–98 counties of six high endemicity provinces	Stomach cancer mortality rate	Schistosomiasis mortality rate	Males, significant positive correlation in three provinces Females, positive correlation in four provinces ($p < 0.05$ in two)
		Oesophageal cancer mortality rate	Schistosomiasis mortality rate	Males, significant positive correlation in two provinces Females, positive correlation in five provinces ($p < 0.05$ in one)
		Liver cancer mortality rate	Schistosomiasis mortality rate	Males, significant positive correlation in one province; Females, significant positive correlation in five provinces ($r = 0.22$, 0.24, 0.32, 0.39, 0.44)
		Colorectal cancer mortality rate	Schistosomiasis mortality rate	Males, $r = 0.36$, 0.49, 0.58, 0.71, 0.81, 0.89 (all $p < 0.05$) Females, $r = 0.23$, 0.41, 0.44, 0.74, 0.85, 0.85 (all $p < 0.05$)

Table 3 (contd)

Reference	Population observed	Outcome index	Exposure index	Geographical correlations
Guo *et al.* (1984)	China, 7 counties of Jiangsu Province	Stomach cancer mortality rate	Schistosomiasis mortality rate	$r = -0.268, p < 0.001$ Inverse correlation with infection prevalence rate
		Oesophagus mortality rate	Schistosomiasis mortality rate	$r = 0.059, p \geq 0.20$
		HCC mortality rate	Schistosomiasis mortality rate	$r = 0.0053, p \geq 0.50$
		Colorectal cancer mortality rate	Schistosomiasis mortality rate	$r = 0.630, p < 0.001$ Direct correlation with infection prevalence rate
Xu & Su (1984)	China, 89 communes in 4 high-prevalence counties, Jiangsu Province 1977–79	Colorectal cancer mortality rate	Estimated *S. japonicum* infection prevalence rate	$r = 0.68, p < 0.01$
	24 communes, Haining county, Zhejiang Province	Colorectal cancer incidence rate	*S. japonicum* survey prevalence rate	$r = 0.60, p < 0.01$ (separately, colon, $r = 0.42$; rectum, $r = 0.48$)
Guo *et al.* (1985)[a]	China, Haining county, Zhejiang Province	Colorectal cancer mortality rate	*S. japonicum* survey prevalence rates	–
Li (1988)	China, 12 provinces in south	Colorectal cancer mortality	Incidence rate of schistosomiasis	$r = 0.71, p < 0.01$
	10 counties of Jiaxing area of Zhejiang Province	Colorectal cancer mortality	Incidence rate of schistosomiasis	$r = 0.90, p < 0.001$
	4 groups of counties in Jiaxing Prefecture	Colorectal cancer mortality	Incidence rate of schistosomiasis	$r = 1.00, p > 0.05$
Guo *et al.* (1993)	China, 49 rural counties selected on the basis of diversity of mortality from selected cancers	Colorectal cancer mortality rate	Schistosomiasis mortality rate	Univariate: males, $r = 0.395$, $p < 0.01$; females, $r = 0.538$, $p < 0.01$ Multivariate standardized: males, $r = 0.333, p < 0.01$; females, $r = 0.537, p < 0.01$

HCC, hepatocellular carcinoma; *, significant

[a]Correlation not formally tested

positive correlation between the prevalence of infection and mortality from either stomach or oesophageal cancer was found in the counties in Jiangsu Province.

(*c*) *Colorectal cancer*

In the study of Liu *et al.* (1983), mortality from colorectal cancer was correlated with that from schistosomiasis (r = 0.695 for men and 0.625 for women) in 24 Chinese provinces. In the analysis by county, significantly positive correlations were found for people of each sex in all six provinces (r, 0.23–0.89; median, 0.61).

Colorectal cancer mortality was correlated with 'prevalence of infection' (r = 0.63 for the two sexes combined) in seven counties in Jiangsu (Guo *et al.*, 1984); and the prevalence of infection was correlated with cancer mortality (r = 0.68) in the 89 communes of four high-prevalence counties in the Province (Xu & Su, 1984) and with cancer incidence (r = 0.42 for colon, 0.48 for rectum, 0.60 overall) in 24 communes of Haining County, Zhejiang Province (Xu & Su, 1984). Mortality from colorectal cancer was correlated with the incidence of schistosomiasis in 12 provinces of South China (r = 0.71), in 10 counties of the Jiaxing area of Zhejiang Province (r = 0.90) and in four county groups in Zhejiang Province (r = 1.00) (Li, 1988). Although in the latter analyses concern was raised about covariation between schistosomal infection and low levels of dietary selenium, in none of the above were dietary or other possible causes of colorectal cancer taken into consideration.

In a large correlation study from China, 65 rural counties were selected on the basis of the diversity of mortality rates from selected malignancies in an attempt to examine links between cancer mortality in 1973–75 and the dietary habits in 1983 of carefully selected, representative inhabitants (Chen *et al.*, 1990). The correlation between mortality rates for colorectal cancer and those for schistosomiasis was formally examined in a regression analysis, with adjustment for estimated consumption of individual nutrients and micronutrients. A significant association (r = 0.89, $p < 0.001$) was found. The correlation was significant for mortality from cancers of both colon (0.72) and rectum (0.88) when they were analysed in a subset of 49 counties. In both studies, the strength of the relationship between mortality from schistosomiasis and from cancer was as strong and consistent as that between mortality from schistosomiasis and any other variable. In a separate analysis of mortality from colon cancer by sex, significant associations with mortality from schistosomiasis were found for both men and women (Guo *et al.*, 1993).

While decades have passed since the first substantial efforts were made to control *S. japonicum* infection, no serious attempt has been made to assess the impact of eradication on the incidence of colorectal cancer. In one area, the continued high incidence of colorectal cancer has been attributed to the large number of people with controlled, advanced schistosomiasis (Guo *et al.*, 1985).

2.2 Case reports and case series

The first suggestion of a link between schistosomiasis and cancer came from careful assessment of clinical and pathological observations (Goebel, 1905; Ferguson, 1911; Kazama, 1921); however, as knowledge of the distribution and presentation of both schistosomiasis and cancer has accumulated, it has become apparent that case reports and

series cannot help in assessing cancer etiology. In endemic areas, substantial proportions of the population are infected. Moreover, evidence of infection is widely disseminated throughout the body, remains there throughout life and may or may not produce symptomatic disease. Under the null hypothesis of no association between infection and cancer occurrence, it is therefore to be expected that a substantial proportion of the population of all ages will have been among those with clinical or subclinical disease, that a substantial proportion of patients with newly diagnosed cancer will show evidence of past infection, that evidence of infection may appear in virtually any organ of the body, and that such evidence of infection may therefore be expected to be incorporated in or found adjacent to virtually any tumour. Nonetheless, cases and case series can add credibility to the evidence of a causal relationship between these infections and cancer by documenting the anatomical proximity of the effects of infection to the appearance of the malignancy and by illustrating changes in the clinical and pathological characteristics of malignancies as they appear in conjunction with the infection.

2.2.1 *Schistosoma haematobium*

Subsequent to the early reports, large series of cases of urinary bladder cancer have been reported in association with evidence of *S. haematobium* infection (see Box).

The case descriptions have repeatedly emphasized the preponderance of squamous-cell urinary bladder tumours among cases with evidence of schistosomal infection, the somewhat different distribution over the surface of the bladder (notably the rarity of occurrence in the trigone) in comparison with bladder tumours in developed countries, and the prevalence of metaplastic changes in conjunction with evidence of infection (da Silva Lopes, 1984). Clinically, the most notable and consistent feature described in these series is the relative youth of the cases with evidence of a link to *S. haematobium* infection. While this observation is made in almost all of the reports, and is usually interpreted as constituting evidence of etiological heterogeneity, the finding does not constitute strong evidence because evidence of the infection is known to decrease in frequency with age.

Other than urinary bladder cancer, the malignancies most frequently reported in association with *S. haematobium* infection are those of the female genitalia. A few dozen cases of squamous cervical carcinoma have been reported from endemic areas (Badawy, 1962; Youssef *et al.*, 1962; Berry, 1966; Sharma *et al.*, 1970; Youssef *et al.*, 1970; Bognel *et al.*, 1980; Schwartz, 1984; El Tabbakh & Hamza, 1989), and the same authors and others (Shafeek, 1957; Iskander & Kamel, 1968; Sunder-Raj, 1976; Al-Adnani & Saleh, 1982; El-Maraghy *et al.*, 1982) have reported certain other genital squamous malignancies, ovarian cystadenocarcinomas, Brenner tumours and teratomas. It has been alleged that breast cancers in men infected with *S. haematobium* constitute a relatively high proportion of all male breast cancers in Egypt (El-Gazayerli & Abdel-Aziz, 1963; Sherif *et al.*, 1980), but the reported numbers are small and cannot be evaluated. Relatively small numbers of other malignancies that have been reported in association with evidence of *S. haematobium* infection include hepatocellular carcinoma (Nkrumah, 1964; Hashem, 1971), bladder sarcoma (Alwan *et al.*, 1988) and lymphomas (Edington *et al.*, 1970; Cheever *et al.*, 1978).

Angola (da Silva Lopes, 1984)
Egypt (Mohamed, 1954; Mustacchi & Shimkin, 1958; El-Gazayerli & Khalil, 1959; Hashem *et al.*, 1961; Aboul Nasr *et al.*, 1962; Makhyoun *et al.*, 1971; El-Bolkainy *et al.*, 1972; Khafagy *et al.*, 1972; El-Sebai, 1980; El-Bolkainy *et al.*, 1981; Christie *et al.*, 1986a; Tawfik, 1988; Fukushima *et al.*, 1989)
Senegal (Quenum, 1967)
Zambia (Bhagwandeen, 1976; Elem & Purohit, 1983)
Nigeria (Attah & Nkposong, 1976), Malawi (Lucas, 1982b)
Sudan (Malik *et al.*, 1975; Sharfi *et al.*, 1992)
Kenya (Anjarwalla, 1971; Bowry, 1975)
Iraq (Al Adnani & Saleh, 1983; Al-Fouadi & Parkin, 1984)
Natal (Cooppan *et al.*, 1984)
South Africa (Transvaal) (Higginson & Oettlé, 1962; Hinder & Schmaman, 1969; Kisner, 1973)
Uganda (Dodge, 1962)
Saudi Arabia (Cutajar, 1983; Hanash, 1984; Khurana *et al.*, 1992)
Kuwait (Al-Shukri *et al.*, 1987)
Mozambique (Prates & Gillman, 1959; Gillman & Prates, 1962; Ebert, 1987)
United Republic of Tanzania (Kitinya *et al.*, 1986)
Zimbabwe (Houston, 1964; Gelfand *et al.*, 1967; Thomas *et al.*, 1990) and
Among immigrants in Europe (Wagenknecht, 1974; Pieron *et al.*, 1983; Delmas *et al.*, 1986) or visitors to Africa (Diaz Hernandez *et al.*, 1984).

2.2.2 *Schistosoma mansoni*

Cases of liver cancer have been reported in connection with evidence of *S. mansoni* infection from Egypt (Hashem, 1971), Mozambique (Prates & Torres, 1965), Brazil (Cheever & Andrade, 1967; Lyra *et al.*, 1976), Puerto Rico (Martinez-Maldonado *et al.*, 1965), Saudi Arabia (Nouh *et al.*, 1990) and Nigeria (Edington *et al.*, 1970). Similarly, cases of colorectal cancer have frequently been described from Egypt (Afifi, 1948; Dimmette *et al.*, 1956; Cheever *et al.*, 1978) and Lebanon (Uthman *et al.*, 1991). Andrade and Abreu (1971) reported the occurrence of eight giant follicular lymphomas in 863 spleens removed from patients with portal hypertension due to infection with *S. mansoni*; subsequently, six additional cases of this neoplasm were described (Paes & Marigo, 1981) in a similar series of 714 spleens. Of these 14 lymphomas, four were further confirmed in biopsy samples or at autopsy; the rest were lost to follow-up. Although other individual cases of diverse lymphomas have been reported in patients with schistosomiasis (Andrade & Abreu, 1971; Cheever *et al.*, 1978; de Andrade *et al.*, 1982; Chirimwami *et al.*, 1991), no reports of giant follicular-cell lymphoma have subsequently appeared.

Other malignancies that have been reported in association with evidence of *S. mansoni* infection include prostatic cancer (Alexis & Domingo, 1986; Godec *et al.*, 1992), ovarian

teratoma (Kahn *et al.*, 1978), uterine leiomyosarcoma (Joyce *et al.*, 1972), renal-cell carcinoma (Oro Ortiz *et al.*, 1991), rectal carcinoid tumour (Satti *et al.*, 1988) and cancer of the cervix (Coelho *et al.*, 1979; Wright *et al.*, 1982).

2.2.3 *Schistosoma japonicum*

Most of the cases or series of cases of liver cancers reported in association with *S. japonicum* infection have come from Japan (Iuchi *et al.*, 1971; Nakashima *et al.*, 1975; Kojiro *et al.*, 1986; Fujimoto *et al.*, 1989; Kitani & Iuchi, 1990; Uetsuji *et al.*, 1990). Within such series, cases of liver cancer have been reported to occur commonly in patients who responded positively to a skin test or were shown histologically to have *S. japonicum* infection (Iuchi *et al.*, 1971; Nakashima *et al.*, 1975; Kojiro *et al.*, 1986); in patients who had evidence of hepatitis viral infection (Nakashima *et al.*, 1975; Kitani & Iuchi, 1990; Kojiro *et al.*, 1986); and in those with schistosoma-associated cirrhosis (Iuchi *et al.*, 1971; Kitani & Iuchi, 1990). In one small series from an endemic area, *S. japonicum* was not found to be especially common in cases of liver cancer (Kamo & Ebato, 1982).

Series of cases of gastric cancer associated with histological evidence of *S. japonicum* infection have been reported from both Japan (Amano, 1980) and China (Wang, 1979; Qian & Yi, 1980; Feng & Shi, 1981; Wang & Kuang, 1983; Zhou, 1986).

Series of cases of colorectal cancer found in association with infection with *S. japonicum* have been reported from Japan (Shindo, 1976; Inoguchi *et al.*, 1978; Naito *et al.*, 1979; Amano, 1980; Hashimoto *et al.*, 1986; Sekiguchi *et al.*, 1989), the Phillipines (Abanilla, 1986) and China (Chen & Chen, 1957; Tsou & Ying, 1958; Wu *et al.*, 1960; Chuang *et al.*, 1979; Chen *et al.*, 1980; Chen *et al.*, 1981; Zhao & Wong, 1981; Liu *et al.*, 1983; Zhuang *et al.*, 1985; Chen, 1986). As in studies of bladder cancer, schistosomally infected patients are of younger average age in most series (Abanilla, 1986; Chen, 1986). This observation is difficult to interpret in the light of differences in the prevalence of infection with age.

Other malignancies that have been reported as individual cases in relation to *S. japonicum* infection include squamous-cell carcinoma of the skin (Ohtake *et al.*, 1991), malignant schwannoma (Schwartz, 1982), carcinoma of the parotid gland (Tangchai & Poshayalakshana, 1968), bronchogenic carcinoma (Ishihara *et al.*, 1984) and breast cancer (Zhou, 1983).

2.3 Cohort study

Inaba (1984) categorized all 2067 people native to a locality in Yamanashi Prefecture, Japan, endemic for *S. japonicum* infection into four classes, depending on whether they had resided before 1957 in that place for more than 50 years, 30–49 years, 10–29 years or fewer than 10 years (Table 4). Duration of residence was taken as an indicator of extent of exposure. They were then followed in the locality-based registers available in Japan, and all death certificates were collected. There were 26 deaths from liver cancer and 16 from colorectal cancer (nine from colon cancer). It was found that men who had lived for more than nine but less than 50 years in a community had a significantly high risk of liver cancer, and that women living in the community for 50 or more years had a significantly high risk of colorectal cancer. No adjustment was made for diet or for hepatitis viral infection.

Table 4. Cohort study of cancer based on death certificates for natives of a town in Yamanashi Prefecture, Japan, endemic for *S. japonicum* infection

Length of residence before 1957 (years)	Number of exposed subjects	Cancer	Number of cases	SMR	
				Males	Females
0–9	428	Liver	1	0.81	–
10–29	575		9	3.2[a]	2.5
30–49	655		10	2.9[a]	1.1
≥ 50	404		6	1.8	0.88
0–9	428	Colon	0	–	–
10–29	575		2	–	2.0
30–49	655		4	2.4	1.9
≥ 50	404		3	–	4.6[a]

From Inaba (1984); SMR, standardized mortality rate
[a] 95% confidence interval excludes 1.0

2.4 Case–control studies (with retrospective exposure assessment)

2.4.1 *Schistosoma haematobium*

Mustacchi and Shimkin (1958) identified 48 male and 7 female hospitalized patients with urinary bladder cancer in the Egyptian Nile Delta city of Tanta among 1472 consecutive admissions to the hospital. All patients were evaluated in relation to the presence of *S. haematobium* eggs in a urine sample taken at admission and to any subsequent evidence of *S. haematobium* infection [the latter but not the former could have been obtained on the basis of knowledge of the presence of bladder cancer]. After multivariate adjustment for age, sex and urban or rural origin, odds ratios of 2.1 ($p = 0.04$) were seen for the finding of eggs at the time of admission and 2.2 ($p < 0.01$) for any subsequent evidence of schistosomal infection.

Prates and Gillman (1959) compared 100 urinary bladder cancer cases in Maputo, Mozambique, with 185 cases found at autopsy in people over 40 years of age with respect to the frequency of identification of *S. haematobium* eggs in relation to the histological type of bladder cancer. Eggs were found in 33 of the cases found at autopsy and in 61% of controls [odds ratio, 0.3; 95% confidence interval (CI), 0.2–0.5]. Eggs were found in 56% of the 59 squamous-cell cancer patients but in none of the transitional-cell cancer patients. [The methods used to examine the biopsy and autopsy specimens were dissimilar, and there was no reconciliation of the high rate in cadavers, despite the absence of eggs in the bladders of people with transitional-cell cancer. The causes of death of the controls were not described, and no adjustment was made for differences in specific age or place of origin.]

Hinder and Schmaman (1969) compared the prevalence of histologically identified eggs in punch biopsy specimens from 79 patients with urinary bladder carcinoma in Johannesburg, South Africa, with the prevalence in two or more full-thickness biopsy specimens from 101 people over the age 15 who came to autopsy. Eggs were identified in 34.2% of the cases but in only 9.0% of the autopsied patients [odds ratio, 5.3; 95% CI,

2.3–12]. The causes of death of the controls were not provided, and no adjustment was made for differences in specific age or place of origin. When cases were analysed by histological type, 19% of transitional-cell carcinomas and 68% of squamous-cell carcinomas contained eggs.

Gelfand *et al.* (1967), in Harare, Zimbabwe, compared 33 patients with urinary bladder cancer with other hospital patients who had been 'submitted to similar investigation' and were matched on age, sex and race. Comparisons were made on the basis of the results of pelvic X-rays (33 pairs) and rectal biopsies (31 pairs). Among the 16 pairs discordant for calcified eggs identified by X-ray, the case was positive in 15, giving an odds ratio of [15; 95% CI, 2.0–114]; among the 15 pairs discordant for the results of rectal biopsy, the case was positive in 13, giving an odds ratio of [6.5; 95% CI, 1.5–29]. The diagnoses of disease in the controls were not described, and no adjustment was made for differences in smoking habits or place of origin.

In a project for cytological screening of urinary bladder cancer conducted from 1976 to 1979 in a location in the Nile Delta highly endemic for *S. haematobium*, participants over 20 years of age were characterized by occupation, on the presumption that the 4769 agricultural labourers in this age group had a higher prevalence of infection than 1112 people with other occupations (El-Bokainy *et al.*, 1982). All 10 cases of bladder cancer detected and confirmed histologically appeared among the agricultural workers [prevalence ratio, ∞]. Although the ages of the subjects were not analysed in detail, it was concluded that adults of this working class were at increased risk of bladder cancer.

In Zambia, Elem and Purohit (1983) compared the bladders of 50 patients who had died of urinary bladder cancer with bladders from age- and sex-matched cadavers (mostly trauma victims matched on age and sex to the decedent) by means of X-ray examination and digestion of tissues away from the eggs they contained. The bladders of the cases were [3.8] [95% CI, 1.4–10] times as likely to show schistosomiasis by X-ray and [14] [95% CI, 4.6–43] times as likely to contain *S. haematobium* eggs.

In the Bulawayo region of Zimbabwe, cancer registration procedures from 1963 to 1977 included collection of information about exposures, including past history of clinical schistosomiasis ('bilharzia' or 'blood in the urine') (Skinner *et al.*, 1993). Some difference in the availability of information about past schistosomiasis is evident between cases of urinary bladder cancer (61%) and cases of cancer of other types (50%). The exposures of 305 patients with bladder cancer were compared with those of 3145 other cancer patients, with and without exclusion of people with cancers known to be linked to smoking. The occurrence of bladder cancer was associated with place of origin, a lower level of education and a more menial occupation. No effect of smoking was found for squamous-cell cancers and only a modest effect (1.3) for other cancers. For a history of schistosomiasis in men, the odds ratio (using all other cancer cases as controls, relative to no such history and adjusted for age, tobacco use, province of origin, education and occupation) was 3.9 (95% CI, 2.9–5.1) for all types of cancer and 3.4 for both squamous-cell cancer and other specified carcinomas. When the cases of smoking-related cancers were excluded from the control group, the odds ratio for squamous-cell cancers increased to 3.9 and that for other cancers dropped to 3.1.

These studies are summarized in Table 5.

Table 5. Case–control studies of infection with *Schistosoma haematobium* and urinary bladder cancer

Reference	Location	Source of cases	Source of controls	Measure of exposure	No. of cases/ no. of controls	Cases/controls exposed (%)	Odds ratio	95% CI (or *p*)	Cases with squamous-cell tumours (%)
Mustacchi & Shimkin (1958)	Tanta, Nile Delta, Egypt		Other admissions to hospital	Eggs in first urine sample	55/1417	14.5/7.6	2.1[a]	0.04	Not specified
				All clinical evidence, including history and cystoscopy	55/1417	49.0/23.3	2.2[a]	< 0.01	
Prates & Gillman (1959)	Maputo, Mozambique		Autopsied people > 40 years	Eggs identified in histological sections	100/185	33/61.1	[0.3	0.2–0.5]	59 (56 with past exposure)
Hinder & Schmaman (1969)	Johannesburg, South Africa		Autopsied people > 15 years	Post-mortem punch biopsy sample	79/101	34.2/9.0	[5.3	2.3–12]	28 (68 with past exposure)
Gelfand *et al.* (1967)	Harare, Zimbabwe		Matched patients[b] of same age, sex, race, on different hospital ward	Pelvic X-ray	33/33	45.5/3.03	[15	2.0–114]	62 (62 with past exposure)
				Rectal biopsy	31/31	54.8/19.4 (discordant matched pairs 1) 15/1 2) 13/2)	[6.5	1.5–29]	
El-Bolkainy *et al.* (1982)	Dakahliya Governorate, Nile Delta, Egypt	Rural residents participating in a bladder screening programme subdivided by occupation		Occupation as farmer	10/5871	100/81	∞		50
Elem & Purohit (1983)	Lusaka, Zambia		Cadavers without malignancy (mostly traumatic death)	Digestion and centrifugation of bladder	50/50	94.0/40.0	[14	4.6–43]	72
				Pelvic X-ray	50/50	38/14	[3.8	1.4–10]	
Skinner *et al.* (1993)	Bulawayo, Zimbabwe	Cancer registry cases, males	Registry cases with other cancers	Self-reported history of bilharzia or blood in urine	305/3145	348/11.7	3.9[c]	[2.9–5.1]	71. No change when tobacco-related cancers excluded from controls

[a]Adjusted for age, sex and urban or rural residence

[b]Who were 'submitted to same procedure'

[c]Adjusted for age, period, province, drinking and smoking

Of interest is an additional case–control study of urinary bladder cancer, which was not performed to test the hypothesis of schistosomal etiology (Table 6). Makhyoun (1974) compared males admitted to hospital for urinary bladder cancer in Alexandria and Tanta, Egypt, with other admitted males, matched on age and smoking history, after stratification of cases and controls on the basis of history of clinical schistosomiasis. In 80% of people without such a history who had smoked heavily or moderately, the malignancies were strongly associated with cumulative smoking history. Only 23% of the schistosomiasis patients had smoked moderately or heavily, and the link between cancer and smoking in these subjects, while present, was weaker. [While the role of past clinical schistosomiasis in bladder cancer was not assessed within groups comparable for past smoking history, the low level of smoking among the patients with *S. haematobium*-associated cancer makes it extremely unlikely that the pattern of smoking could explain the strong links between infection and bladder cancer.]

Table 6. Case–control study of urinary bladder cancer in relation to smoking and history of infection with *Schistosoma haematobium* among males admitted to hospital

Infection status	Smoking index[a]	No. exposed		Odds ratio
		Cases	Controls	
History of *S. haematobium* infection	None	66	80	1.0
	Light (< 300)	149	145	1.3
	Moderate (300–600)	42	35	1.5
	Heavy (> 600)	21	18	1.4
	Moderate–heavy	63	53	1.4
No history of *S. haematobium* infection	None	15	23	1.0
	Light (< 300)	3	24	0.2
	Moderate (300–600)	41	27	2.3
	Heavy (> 600)	28	13	3.3[b]
	Moderate–heavy	69	40	2.6[b]

From Makhyoun (1974); odds ratios calculated by the Working Group.
[a]Daily number of cigarettes times number of years smoking
[b]Significantly different at $p < 0.01$

2.4.2 *Schistosoma japonicum*

In a comparison based on skin testing for antigens to *S. japonicum*, Iuchi *et al.* (1971) found that 85.2% of 52 cases of hepatocellular carcinoma and 68.2% of 217 other hospital in-patients over 40 years of age had antigens. No adjustment was made for evidence of past hepatitis viral infection.

Inaba *et al.* (1984) used skin testing and medical histories to compare 62 cases of liver cancer diagnosed in seven hospitals in an endemic area, Yamanashi Prefecture, Japan, in 1977–79 with age- and sex-matched hospital controls admitted for various diseases other than liver disease. While the univariate relative risk was 9.5 [95% CI, 2.2–41], restriction of the analysis to the 88 subjects seronegative for hepatitis B surface antigen and their controls gave a relative risk of [6.7; 1.5–30] for 39 alcohol users and of [4.7; 1.2–19] for 49 non-users.

Guo and Lu (1987) compared 166 patients who had died of liver cancer with 166 people who had died from other cancers and with 166 healthy people, both groups matched on age, sex and place of residence with respect to a history of *S. japonicum* infection. The matched odds ratio for schistosomal infection based on both series of controls was 2.2 ($p < 0.01$). Relative risks of [2.5; 95% CI, 1.4–4.4] and [2.3; 1.3–4.1] were found in relation to cancer decedents and healthy controls, respectively, after adjustment for smoking and family history of liver cancer but not for evidence of hepatitis viral infection. The relative risk estimates increased significantly with the interval since diagnosis of schistosomiasis, whether cancer or healthy controls were used. Dietary exposure to aflatoxins was considered not to be prevalent in this area.

Amano (1980) compared 362 patients with stomach cancer who were treated surgically in Yamanashi Prefecture, Japan, with 897 surgical cases with non-malignant disease of the stomach and duodenum, and found *S. japonicum* eggs [1.8] [95% CI, 1.3–2.6] times more frequently in the tissues of cases than in those of controls. No adjustment was made for potential confounders. In the same study, eggs were found [1.2] [0.62–2.5] times more often in the tissues of 103 colon cancer cases than in the 96 controls with benign disease of the colon. No adjustment was made for diet or other potential confounders.

In endemic Kunshan County in Jiangsu Province, China, Xu and Su (1984) gathered medical histories on schistosomiasis for all colorectal cancer patients and for patients with other cancers and from healthy neighbours, each matched on age, sex, occupation and work unit. While no significant association was found between colon cancer and past history, odds ratios of 8.3 and 4.5 were found for rectal cancer in comparisons with cancer controls and healthy controls, respectively. No adjustment was made for diet or other potential determinants of colorectal cancer.

In the same county, Guo *et al.* (1987) compared people who had died of colon cancer with those who had died of lung cancer and with healthy people, with respect to any medical history of early- or late-stage schistosomiasis. In relation to healthy controls, odds ratios of 2.4 [CI not given] were found for a history of early-stage infection and 5.5 [CI not given] for a history of late-stage schistosomal disease. After adjustment for smoking and a family history of colon cancer, but not for diet or exercise, significant associations were still found: 2.1 (95% CI, 1.1–3.8) and 4.2 (1.2–15) in relation to lung cancer controls for early- and late-stage disease, respectively, and 2.4 (1.1–5.0) and 5.7 (1.3–25) for the same exposures in relation to healthy controls. The risk was found to increase stepwise from 1.2 to 4.3 after < 10 years to > 30 cumulative years of infection [CI not given].

These studies are summarized in Table 7.

A number of studies have addressed the association between infections with *S. mansoni* and *S. japonicum* and cancer of the liver. The possible confounding of schistosomal infection with hepatitis viral infection (see IARC, 1994) in these studies has rarely been addressed empirically. A recent review of the coincidence of infection with hepatitis B virus and with *S. mansoni* and *S. japonicum* in population-based studies (Chen *et al.*, 1993) showed no significant increase in the prevalence of hepatitis B surface antigenaemia in people with these schistosomal infections. The prevalence of joint infection is, however, higher in hospital patients than in members of the corresponding general population; in particular, patients hospitalized with hepatosplenic schistosomiasis are more likely to be seropositive

Table 7. Case–control studies of infection with *Schistosoma japonicum* and cancer

Reference	Location	Source of cases	Source of controls	Measure of exposure	Number of cases/controls	Exposure in cases/controls	Odds ratio	95% CI
Liver cancer								
Iuchi *et al.* (1971)	Kofu, Yamanashi Prefecture, Japan	Previous diagnoses in hospital autopsies	Other in-patients	Skin test for *S. japonicum*	61/303	Prevalence of + 91.8%/53.1%	[9.9]	[3.9–25]
				Histology	61/21	91.8%/71.4%	[4.5]	[1.2–17]
Inaba *et al.* (1984)	Yamanashi Prefecture, Japan	Diagnoses in 7 hospitals, 1977–79	Patients matched on sex, age, hospital	Skin test for *S. japonicum*; medical history	62/62		9.5	[2.2–41]
						Negative for hepatitis B surface antigen, alcohol use	[6.7]	[1.5–30]
						Negative for hepatitis B surface antigen, no alcohol use	[4.7]	[1.2–19]
Guo & Lu (1987)	Kunshan County, Jiangsu Province, China	Liver cancer deaths, 1982–83	Deaths from other cancers 'Healthy people', matched on age, sex, county of residence	History of infection	166/166/166		Matched odds ratio, 2.2 ($p < 0.01$); unmatched [1.9 for cancer controls],	[1.1–3.3]
							[2.1 for healthy controls]	[1.2–3.7]
							After adjustment for smoking and family history of liver cancer, odds ratio of [2.5] for cancer controls	[1.4–4.4]
							and [2.3] for healthy controls	[1.3–4.1]
Stomach cancer								
Amano (1980)	Kofu, Yamanashi Prefecture, Japan	Surgically treated hospital cancer patients	Non-malignant cases	*S. japonicum* eggs in pathological specimens	362/897	15.2%/9.0% prevalence	[1.8]	[1.3–2.6]

Table 7 (contd)

Reference	Location	Source of cases	Source of controls	Measure of exposure	Number of cases/controls	Exposure in cases/controls	Odds ratio	95% CI
Colorectal cancer								
Amano (1980)	Kofu, Yamanashi Prefecture, Japan	Surgically treated hospital colon cancer patients	Non-malignant cases	*S. japonicum* eggs in pathological specimens	103/96	22.3%/18.8% prevalence. Much higher differential among those aged 40–49	[1.2]	[0.62–2.5]
Xu & Su (1984)	Kunshan County, Jiangsu Province, China	Colorectal cancer cases, 1973–79	Non-gastrointestinal cancer patients Neighbours, each matched on age, sex, occupation and production brigade or team	Medical history from patients, relatives, barefoot doctors	98/98/98 (colon) 154/154/154 (rectum)		Colon: odds ratio, 1.2 with other cancer controls; 0.64 with healthy neighbourhood controls Rectum: odds ratio, 8.3 with other cancer controls and 4.5 with healthy neighbourhood controls	[0.48–3.2] (triplets) [0.33–1.2] [3.1–22.6] [1.7–12.1]
Guo *et al.* (1987)	Kunshan County, Jiangsu Province, China	Colon cancer deaths, 1981–83	Lung cancer patients 'Healthy persons'	Medical history	197/205/200		Odds ratio, 2.4 (early-stage disease), 5.5 (late-stage disease) After adjustment for smoking and family history of colon cancer, but not diet or exercise, overall significant association remains: 2.1 and 4.2 for early- and late-stage disease with lung cancer controls, 2.4 and 5.7 with healthy controls After < 10, -20, -30, ≥ 30 years since diagnosis, 1.2, 1.9, 2.9, 4.3 duration–response effects	

for hepatitis B surface antigen than those with latent or intestinal schistosomiasis. These observations suggest that hepatitis B viral infection may confound the association between schistosomal infection and liver cancer in hospital-based studies of individuals. There are no similar data that would allow evaluation of the possibility of confounding between hepatitis C viral infection and schistosomal infection.