REVIEW ARTICLE

Possible association and co-existence of schistosome infection and prostate cancer: A systematic review

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Abstract

Male genital schistosomiasis (MGS) may result in eggs lodged in the prostate causing persistent inflammation that may play a major role in prostate carcinogenesis. Globally, prostate cancer (PCa) is one of the most common cancers and the global distribution of PCa overlaps with that of schistosomiasis infections, suggesting a probable causal relationship. Objectives of this review were to assess evidence of co-existence of schistosomiasis and PCa and possible causal association between the two diseases. Relevant literature published between 1950 and 2019 yielded 20 publications on schistosomiasis and PCa co-existence. *Schistosoma* (*S.*) *haematobium* and *S. mansoni* were associated with MGS manifestation and mostly prostate adenocarcinoma diagnosis. Effects of prostatic MGS infection progressed over time with high *Schistosoma* egg burden thought to contribute to the development of PCa. Causal association and mechanistic pathways of MGS on PCa development and the role of *Schistosoma* eggs on the development of PCa remains unestablished. *(Afr J Reprod Health 2020; 24[4]: 185-197).*

Keywords: Schistosomiasis, prostate cancer, bilharzia, prostatic schistosomiasis, male genital schistosomiasis (MGS)

Résumé

La schistosomiase génitale masculine (MGS) peut entraîner la formation d'œufs dans la prostate, provoquant une inflammation persistante pouvant jouer un rôle majeur dans la carcinogenèse de la prostate. À l'échelle mondiale, le cancer de la prostate (PCa) est l'un des cancers les plus courants et la distribution mondiale du PCa chevauche celle des infections à schistosomiase, ce qui suggère une relation causale probable. Les objectifs de cette revue étaient d'évaluer les preuves de la coexistence de la schistosomiase et de la PCa et une possible association causale entre les deux maladies. La littérature pertinente publiée entre 1950 et 2019 a donné 20 publications sur la schistosomiase et la coexistence de la PCa. Schistosoma (S.) haematobium et S. mansoni ont été associés à la manifestation du MGS et principalement au diagnostic d'adénocarcinome de la prostate. Les effets de l'infection prostatique par le MGS ont progressé au fil du temps avec une charge élevée d'œufs de Schistosoma censée contribuer au développement du PCa. L'association causale et les voies mécanistiques du MGS sur le développement du PCa et le rôle des œufs de Schistosoma sur le développement du PCa restent non établis. *(Afr J Reprod Health 2020; 24[4]:185-197).*

Mots-clés: Schistosomiase, cancer de la prostate, bilharziose, schistosomiase prostatique, schistosomiase génitale masculine (MGS)

Introduction

Schistosomiasis

There are twenty neglected diseases including schistosomiasis in 149 countries, mostly in tropical countries[1]. Schistosomiasis is caused by helminths of the genus *Schistosoma*[2,3]. Six *Schistosoma* species, namely *S. haematobium* that causes urogenital schistosomiasis, *S. mansoni, S. japonicum, S. intercalatum, S. mekongi* and *S. guineensi* that cause intestinal and hepatic

schistosomiasis in humans[4-7].Globally, approximately 800 million people are at risk of contracting schistosomiasis infection and 165 million of those affected are in sub-Saharan Africa[8,9]. *Schistosoma haematobium* and *S. mansoni* are the most prevalent *Schistosoma* species accounting for 112 million (67.5 %) and 54 million (32.5 %) infections, respectively in the sub-Saharan African region[6,8]. Common symptoms of schistosomiasis include haematuria, dysuria, abdominal pain, diarrhea and blood in the stool. *Schistosoma* adult trematode worms can live inside the human body for an average of 3 to 10 years[2]. They evade the immune system using a variety of mechanisms that include acquiring the host antigens on their surface membrane thereby masking the worms against immunological attack[10]. Adult schistosomes produce hundreds to thousands of ova that are excreted in urine or stool daily[11]. However, not all the eggs produced are excreted through either urine or stool; a significant proportion remains logged in the body and they cause disease morbidity[2,6].

Urogenital schistosomiasis

Urogenital schistosomiasis is caused by the eggs released by the *S. haematobium* paired adult trematodes that inhabit the venous plexus surrounding organs of the pelvis causing damage to urinary and genital tissues[10]. Male genital schistosomiasis (MGS), first described in 1911 by Madden is a manifestation of urogenital schistosomiasis that is associated with the presence of ova in the genital organs[12]. Some of the ova penetrate and lodge in the vessel walls of nearby tissues of mainly the bladder, bowel and to a lesser extent the seminal vesicle, *vas deferens*, prostate gland, spermatic cord and the penis[12,13]. The ova trapped in tissue induce chronic granuloma formation and eventually damage organs resulting in various complications[14]; for example, obstructive uropathy predisposes one to bacterial infections and eventually leads to renal dysfunction[2] and systemic pathological effects. Some of the symptoms of urogenital schistosomiasis in men include urethritis, leukocytospermia, orchitis, funiculitis and prostatitis epididymitis[15]. Leutscher *et al.* in 2000 reported the presence of schistosome ova in 43% of the semen samples indicating that genitals are commonly sites for ova deposition in men with urogenital schistosomiasis[16]. Consequently, leukocytospermia up-regulates the cytokine, tumor necrosis factor- alpha (TNF-α) which may induce sperm DNA fragmentation that may cause infertility[17]. Anecdotal data suggest that ova deposition in the prostate gland may be associated with the development of prostate cancer.

Prostate cancer

Prostate cancer (PCa) is a heterogeneous group of malignant tumours and these tumours can be identified and classified using the Gleason's grading system[18,19]. It is a standard histologic and the most prognostic PCa clinical identification system used to characterize how aggressive PCa cells appear microscopically[19,20]. Acinar adenocarcinomas are the most common type of PCa that have prostate carcinomas variants such as ductal, mucinous, signet ring cell and small cell carcinoma[21]. Other types of PCa include urothelial carcinoma, sarcomas and lymphomas[21]. PCa is the most common cancer in many countries such as USA, Australia and Zimbabwe[16,22-24]. PCa has a high morbidity and mortality affecting millions of men all over the world[25]. It is commonly diagnosed in older men because the disease progresses slowly and rarely shows clinical symptoms until later in life[26]. Symptoms of PCa include haematuria, frequent urination, nocturia, dysuria, urinary obstruction, and discomfort during urination, the need to suddenly urinate and pain in various bones where cancer would have spread[23,27]. Risk factors for PCa include genetic predisposition, family history of PCa, ethnic origin, older age, history of sexually transmitted diseases specifically gonorrhea and syphilis, history of prostatitis, lack of ejaculation and chemical exposure through occupation[19,28-33]. In countries where schistosomiasis is endemic, the diagnosis of PCa may be delayed by the presumption that symptoms are due to schistosomiasis and the diseases may co-exist.

Schistosomiasis and cancer

Schistosomiasis results in persistent inflammation and 15% of the global cancer burden is due to inflammation and infectious agents[34].

Schistosomiasis infection causes inflammation that could indirectly play a role in prostate carcinogenesis leading to tumorigenesis in the bladder[35]. Analogous path mechanisms have been described for schistosomiasis associated bladder cancer. Authors have described a sequence involving an immunological response to *Schistosoma* miracidal soluble antigens that may lead to chronic cystitis and squamous metaplasia and to tumorigenesis in the bladder[35,36]. The biochemical impact of schistosomiasis infection results in decreased carcinogen metabolizing enzymes such as glutathione S-transferases (GST) and NDMA-N-demethylase that are responsible for detoxifying androgen compounds such as N-nitrosoamines[37,38]. Decreased enzymes promote carcinogen persistence and could contribute to the evolution of bladder cancer[36,37]. *Schistosoma haematobium* worm/eggs have been reported to release catechol estrogen molecules that downregulate estrogen blocking receptors thus creating a permissive of invasive cancer development[38,39]. These molecules were also reported to have high affinity for DNA resulting in DNA adducts that contribute to cancer evolution[40]. Inflammation usually causes granulomatous lesions that could block venules and promote production of reactive oxygen species (ROS)[41]. An increase in the formation of DNA single strand breaks, due to oxidative damage and higher inducible nitric oxide synthase was found in bladder squamous cell carcinoma (SCC) associated with schistosomiasis than non-schistosomiasis-associated cancers[42]. None of these events due to schistosomiasis infection have been linked to PCa development mechanisms. Figure 1 summarizes the possible events that could trigger cancer development following schistosomiasis infection.

In 2012, the WHO classified *S. haematobium* infection as group a 1-carcinogen agent[43] associated with bladder cancer, which accounts for more that eleven thousand deaths per year[8]. Considering that MGS affects the prostate gland, could analogous mechanisms be at play in the evolution of prostatic carcinoma? It is against this background that we conducted this review to assess the current state of knowledge about schistosomiasis and PCa co-existence.

Objectives of this review were to assess evidence of co-existence of schistosomiasis and PCa and possible causal association between schistosomiasis infections and PCa. Furthermore, we identified gaps for future studies to be conducted to elucidate the nature of association of schistosomiasis infection and the development of PCa.

Methods

Search strategy and selection criteria

A systematic review based on scientific articles published from 1950 to 2020 was conducted. Because initial literature review indicated that there was not much literature on the subject matter, we decided to conduct the search in a long timeframe (1950-2020) to include the largest body of published work on the subject. The literature search was done in PubMed, Web of Science, Google scholar, Scopus and EBSCOhost databases using the Boolean operator "AND" using the following key words sequentially: "schistosomiasis AND prostate cancer", "bilharzia AND prostate cancer", "prostate adenocarcinoma AND schistosomiasis, and "prostate adenocarcinoma AND bilharzia, "prostate carcinoma AND bilharzia", "prostate carcinoma AND schistosomiasis". Secondary source articles were identified through a snowball process of checking references in articles identified through the search and assessing them for inclusion in the review. Articles were included if they matched the following criteria: (i) published in a peer reviewed journal, (ii) reported on both PCa and schistosomiasis (iii) case study/series cases reported (iv) population studies (articles with a defined sample size) on co-existence of schistosomiasis and PCa (v) published in English. Articles were excluded if (i) they were reviews only, (ii) did not report on schistosomiasis and PCa exclusively, (iii) reported on just PCa only and (iv) reported on just schistosomiasis eggs found in the prostate gland.

Data extraction

Data extraction from studies was performed by two authors ETC and TM. The following information was extracted for each selected article: (i) first

author, (ii) year of publication, (iii) study population (if any), (iv) study location (v) summary of the findings, (vi) schistosomiasis species and (vii) PCa histology diagnosis.

Article selection

The review process involved five stages to select manuscripts exclusively on schistosomiasis and PCa illustrated by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram (Figure 2). Twenty full-text articles were deemed eligible for the review.

Analysis of assembled literature

Online database search produced 88 publications using the main search terms: schistosomiasis AND prostate cancer (Figure 2 and Table 1). Four additional articles were identified through the snowball process. After screening through the five stages described above 20 articles were included for full review. These included four original research studies, ten case series/study reports, five case studies that included a review and 1 case study and a systematic review. Of the 20 publications on MGS and PCa identified in the period 1955 - 2020, only 4 reports were published prior to 1990. There was an increase in the publications after the year 2000. Supplementary Figure 1 shows the year and the number of publications on schistosomiasis and prostate cancer co-existence reviewed. Thirteen (65 %) articles on the co-existence of *S. haematobium* ova and PCa were published between 1955 and 2019; 5 (25 %) articles on *S. mansoni* were published in 1985, one (5 %) article was on mixed *S. haematobium* and *S. mansoni* infections while another 1 article could not identify the species. The publications reviewed reported prostatic schistosomiasis from 9 schistosomiasis endemic countries (Brazil, Kuwait, South Africa, Tanzania, Angola, Egypt, Ghana, Nigeria and Zambia), 2 non-schistosomiasis endemic countries (Canada and Unites States of America) and from Iraq a country where schistosomiasis was eradicated. Overall, the articles reviewed were reported from 12 countries in 4 continents, Africa [n = 7; 58 %], Asia [n=2, 17 %], North America [n=2, 17 %] and South America [n=1, 8 %]. Table 1 and Table 2 summarize the articles reviewed from different countries.

Results

Search strategy and selection criteria

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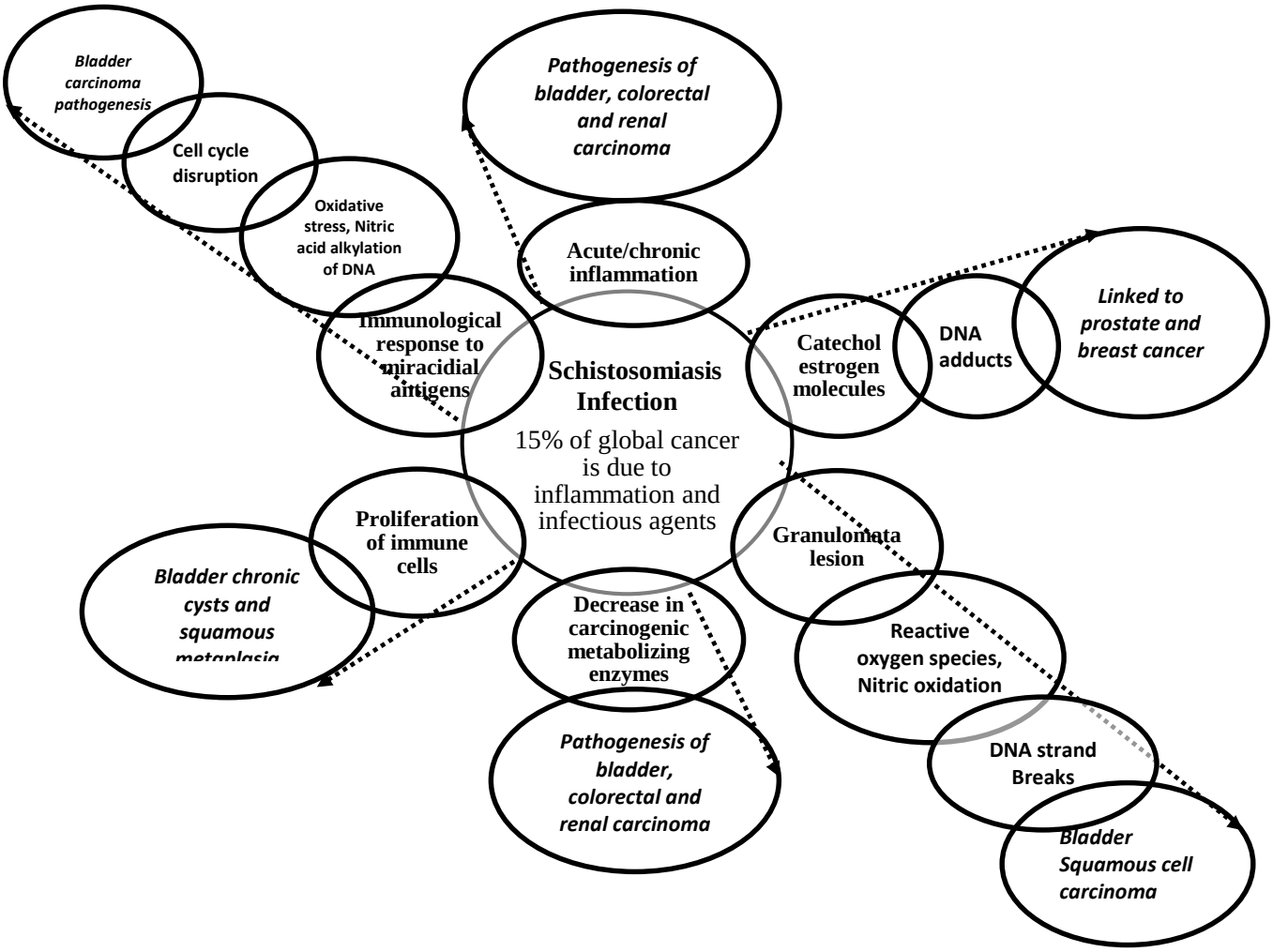

Figure 1: Possible events that could lead to development of cancer due schistosomiasis

(i) first author, (ii) year of publication, (iii) study population (if any), (iv) study location (v) summary of the findings, (vi) schistosomiasis species and (vii) PCa histology diagnosis.

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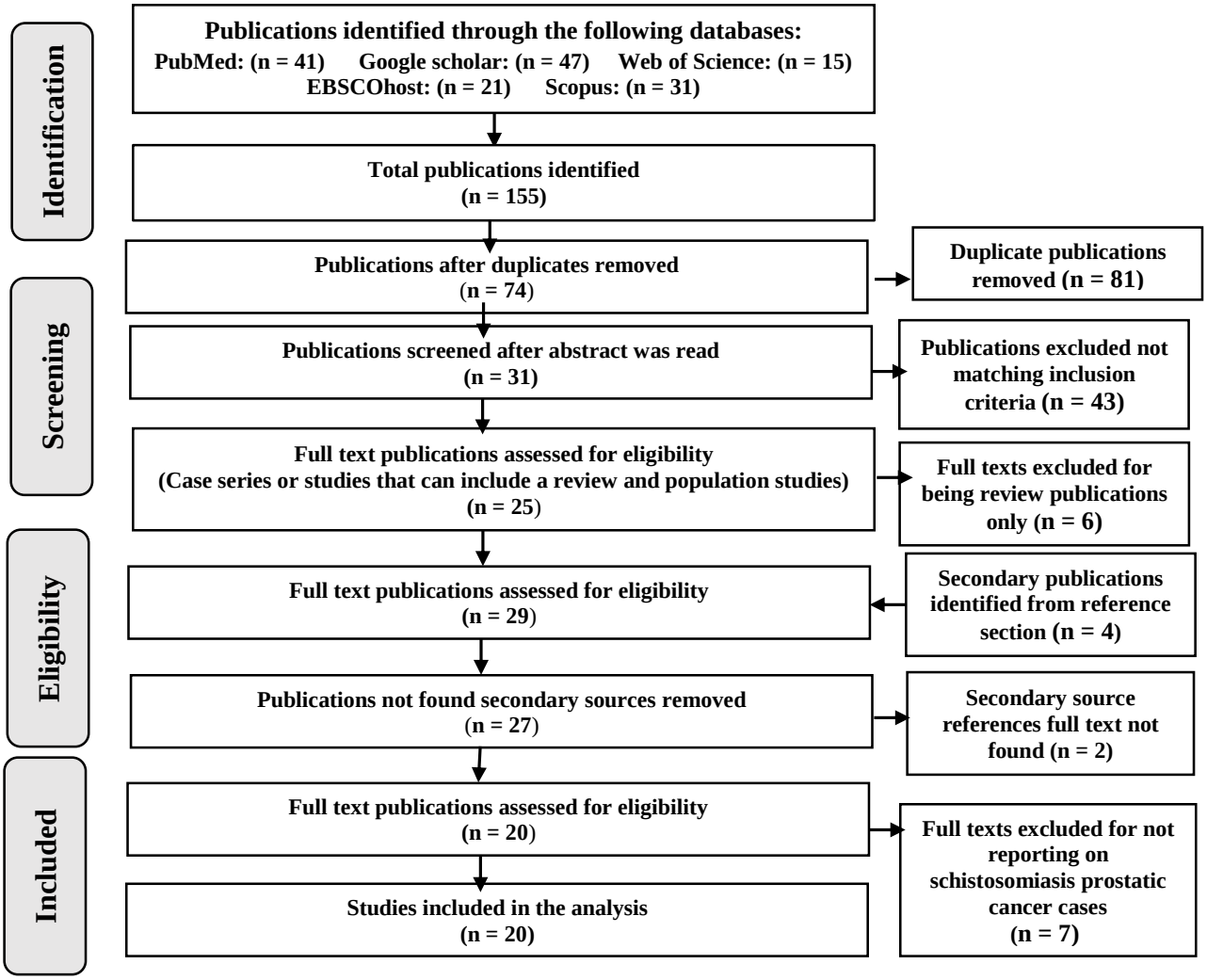


Figure 2: PRISMA flow diagram for reviewed article selection criteria

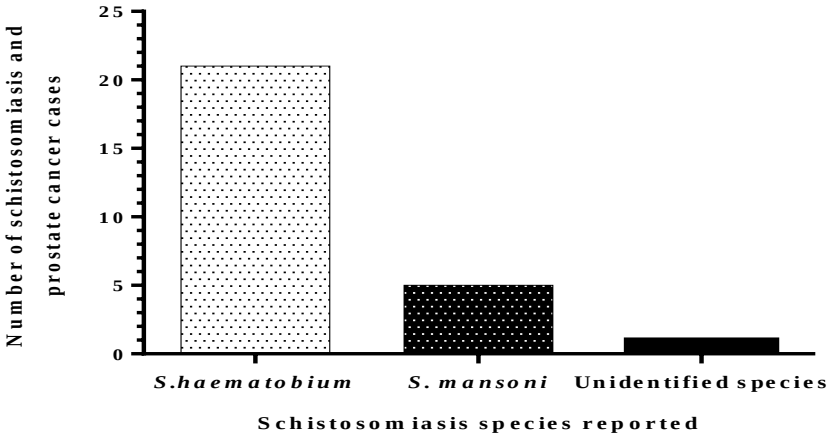


Figure 3: Number of confirmed schistosomiasis prostatic cancer cases and the schistosomiasis species reported
Table 1: Case reports of MGS and PCa

Ref. No.	Author	Country	Year	Patient (s) Age	*Schistosoma* Species	PSA levels	Diagnosis
[44]	Al Adani	Iraq	1985	-	*S. haematobium*	-	2 patients with, Squamous carcinoma of the prostate
[45]	Alexis and Domingo	Brazil	1986	49	*S. mansoni*	-	Prostate adenocarcinoma
[46]	Tungekar *et al.*	Kuwait	1986	-	*S. haematobium*	-	Sarcoma
[47]	Godec *et al.*	USA	1992	49	*S. mansoni*	-	Prostate adenocarcinoma
[48]	Ma and Srigley	Canada (Ghana)	1992	55	*S. haematobium* calcified	9 ng/ml	Adenocarcinoma in peri-adipose tissue and seminal vesicles.
[49]	Cohen *et al.*	South Africa	1995	27, 29, 29	*S. haematobium* Viable and calcified	>100 ng/ml >100 ng/ml 65 ng/ml	Prostate adenocarcinoma
[50]	Basillio-de-Oliveira *et al.*	Brazil	2002	68	*S. mansoni*	9.2 ng/ml	Prostate adenocarcinoma
[51]	Bacealor *et al.*	Brazil	2007	47	*S. mansoni*	9.4 ng/mL	Prostate Adenocarcinoma
[14]	Manasseh *et al.*	Nigeria	2009	70	*S. mansoni*	17.11 ng/ml	Prostate Adenocarcinoma
[52]	Mazigo *et al.*	Tanzania	2010	50, 70, 41	*S. haematobium*	-	Prostate Adenocarcinoma
[53]	Figueiredo *et al.*	Angola	2015	56	*S. haematobium*	>100ng/ml	Malignancy adenocarcinoma
[54]	El-Hawary *et al.*	Egypt	2016	71	*S. haematobium*	10.6 ng/ml, 20ng/ml	Prostatic adenocarcinoma,
[55]	Metrogos *et al.*	Brazil	2017	62	*S. haematobium*	11.59 ng/mL	Prostate adenocarcinoma
[56]	Peiffer *et al*.	USA	2019	Late 40s	*S. haematobium* degenerated	-	Prostate adenocarcinoma
[57]	Mukendi	South Africa	2019	66	*Species undetermined*	14.39 ng/mL	Prostate adenocarcinoma
[58]	Lodhia	Tanzania	2020	66	*S. haematobium*	< 4 ng/mL	Prostate adenocarcinoma

Note: "-"data not reported

Table 2: Population studies reporting on schistosomiasis and prostate cancer

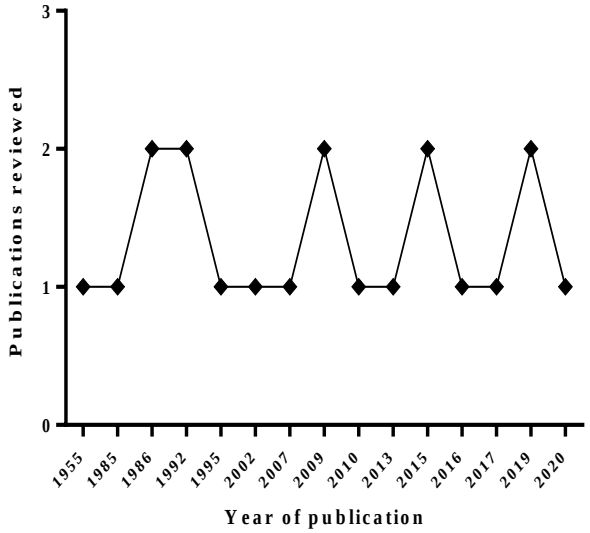
Ref. No.	Author	Country	Year	Sample size	Schistosomiasis species	MGS and PCa outcomes
[59]	Shamma *et al.,*	Iraq	1955	2256	*S. haematobium*	16 cases had prostate and genitalia carcinoma. 3 of these cases had *S. haematobium* ova.
[60]	Mutengo *et al.*	Zambia	2009	58	*S. haematobium*	6 patients of the ages 13, 14, 16, 41, 56 and 70 years had MGS. Two patients had ova in the prostate and 1 patient had both MGS and PCa.
[61]	Okani *et al.*	Nigeria	2013	79	*S. haematobium*	3 patients had schistosomiasis in the prostate and1 had prostate adenocarcinoma.
[62]	Der *et al.*	Ghana	2015	42 340	*S. haematobium* *S. mansoni*	Ova was distributed in the prostate of 3 patients and one case of prostate adenocarcinoma.

2019; 5 (25 %) articles on *S. mansoni* were published in 1985, one (5 %) article was on mixed *S. haematobium* and *S. mansoni* infections while another 1 article could not identify the species.

The publications reviewed reported prostatic schistosomiasis from 9 schistosomiasis endemic countries (Brazil, Kuwait, South Africa, Tanzania, Angola, Egypt, Ghana, Nigeria and Zambia), 2 non- schistosomiasis endemic countries (Canada and Unites States of America) and from Iraq a

Table 3: Number of patient cases, prostate diagnosis and schistosomiasis species reported

Schistosomiasis Species	Prostatic Diagnosis	Number of patient cases
S. haematobium	Adenocarcinoma	15
S. mansoni	Adenocarcinoma	5
S. haematobium	Squamous Cell carcinoma	2
S. haematobium	Sarcoma	1
S. haematobium	Unspecified Carcinoma	4
Total		**27**



Supplementary Figure 1: Year and number of publications on schistosomiasis and prostate cancer co-existence reviewed

country where schistosomiasis was eradicated. Overall, the articles reviewed were reported from 12 countries in 4 continents, Africa [n = 7; 58 %], Asia [n=2, 17 %], North America [n=2, 17 %] and South America [n=1, 8 %]. Table 1 and Table 2 summarize the articles reviewed from different countries.

Discussion

Co-existence of MGS and prostatic carcinoma has only been reported in 20 publications in the last 7 decades. MGS has been primarily reported as a manifestation of urogenital schistosomiasis but MGS morbidity due to *S. mansoni* species has been reported as well[45,47,50,51]. Cases with confirmed MGS associated prostatic cancer did not demonstrate a casual association with carcinogenesis, suggesting this observation may be co-incidental rather than causal. Some patients developed clinical symptoms long after they had been treated for schistosomiasis due to the presence of schistosome ova in prostate. The reported cases had different clinical symptoms implying that no symptoms are unique for schistosomiasis associated prostatic cancer. Whereas, viable or calcified or degenerated tissue lodged schistosomiasis eggs can be linked to prostatic cancer, the presence of *Schistosoma* eggs is not invariably associated with carcinogenesis[56,63].

All but five cases of prostatic cancer have been associated with urogenital schistosomiasis (Table 3) possibly due to the close proximity to the prostate gland to where the *S. haematobium* adult worms reside inside the body. However, cases of intestinal schistosomiasis can possibly result in MGS because the worms and or the eggs may end up in ectopic locations such as the spinal cord[64] and the genital area. This could be so because the adult worms may travel against venous blood flow entering collateral vessels and deposit their eggs at the end venules[65]. The presence of *Schistosoma* eggs in the prostate of individuals without cancer diagnosis has been reported severally over the years and across continents[11,63,66-69]. Even though PCa was not reported in other cases of intestinal schistosomiasis species, *S. japonicum* ova were found in the prostate gland in 2013 by Yu *et al*[70]. The relevance and value of PSA measurements in the screening and or monitoring of prostatic cancer has been subject to debate. Some of the schistosomiasis prostatic cancer cases assessed in this review had high levels of PSA[48,49,53-55]. However, other reported prostatic schistosomiasis cases had high PSA levels and were are not uniquely associated with PCa[12,63,64]. It could be so that high PSA could be due to schistosomiasis prostatic inflammation as opposed to or could be the case of prostate cancer. Schistosomiasis associated prostatic cancer can be asymptomatic[24], hence patients with suspicious symptoms and an elevated PSA in schistosomiasis endemic areas should be investigated. High PSA levels reported in relation to prostatic cancer should prompt clinicians to investigate the possibility of schistosomiasis prostatic cancer.

In South Africa, Cohen *et al*. showed that in the presence of a large number of *Schistosoma* eggs in the prostate, prostate carcinogenesis could occur even in younger men[49]. However, a causal link or association has not been demonstrated. El-Bolkainy[71] showed that individuals with *Schistosoma* eggs developed bladder tumors at a younger age than individuals without the *Schistosoma* eggs. It is therefore plausible that in

individuals that reside in schistosomiasis endemic areas, prostatic tumors may begin at an early age because of the inflammatory processes mediated by *Schistosoma* eggs embedded in the prostate.

In 2015, Elfaki investigated the association of schistosomiasis and PCa by measuring the PSA levels of 50 urogenital schistosomiasis infected participants samples[27]. All the samples were reported negative for PSA hence they concluded that there was no association between urogenital schistosomiasis and PCa. It is not known if the patients with schistosomiasis are likely to develop PCa later on in life as a result of schistosomiasis infection. Botelho *et al*. in 2010 reported that *Schistosoma* eggs produce oestrogenic molecules that are highly carcinogenic[38] and this could explain how schistosomiasis infection can induce prostate carcinogenesis.

Moreover, Tuffour *et al*. in 2018 provided evidence on schistosome infections as a potential etiological agent[72]. They found that schistosome egg antigens induce oncogenic phenotypes including oxidative stress, increased proliferation and diminished apoptosis in cultured normal human prostate cells. Additionally, as schistosomiasis becomes chronic, granulomas are formed, Peiffer *et al*. in 2019 associated regions that are adjacent to granulomatous inflammation in prostate such the proliferative inflammatory atrophy to be induced by urogenital schistosomiasis[56]. Hence, granuloma intermediate cells are suspected target cells for prostate carcinogenesis[56].

The possibility of cancer development due to schistosomiasis and HIV virus co-infection

A pilot study by Midzi *et al*., in 2017 showed a decrease in HIV-1 RNA load in semen of HIV positive men co-infected with urogenital schistosomiasis after praziquantel treatment[73]. Therefore, MGS and HIV co-infected individuals might have an accelerated HIV propagation rate in seminal fluids and plasma which will lead to an increase in viral load and rapid advancement to HIV/AIDS. Schistosomiasis causes constant inflammation, orchestrated by eosinophils and lymphocytes resulting in a great number of activated CD4+ immune cells in the genital fluids[74]. The HIV virus attaches and gains access into other cells leading to an increment in the propagation rate of the virus and destruction of the immune cells that leads to other viral infections[75-77]. The viruses will in turn cause proliferation of the infected cells leading to neoplasms in the infected host that will eventually become cancerous[77].

The burden of MGS infection is underestimated because specific manifestations of urogenital schistosomiasis in adults is unnoticed due to inadequate disease surveillance[77]. Certain individuals with MGS could be under diagnosed in relation to the association of schistosomiasis and PCa, hence detailed epidemiological studies are necessary to elucidate the association between schistosomiasis and PCa. Approximately sixty percent of the publications reviewed on schistosomiasis and PCa have been reported in few countries in Africa where schistosomiasis is endemic suggesting that regional variation should be taken into account for prostatic schistosomiasis carcinoma screening. Despite geographical concurrent distribution of the schistosomiasis and PCa there is no substantial evidence to differentiate PCa development between individuals that reside in schistosomiasis endemic or non-endemic countries. The rarity of the number of cases where schistosomiasis is associated with PCa could be due to lack of mechanistic studies that could elucidate the causal associations of schistosomiasis to the development of PCa. Cohen *et al*. speculated that the association between schistosomiasis and PCa could be due to high *Schistosoma* egg burden[49].

However, the mechanism of how ova lead to PCa remains unknown. MGS might be a co-factor in the aetiology of PCa. Therefore, genetic factors alongside immunological responses to the prostate *Schistosoma* embedded eggs can possibly aid in elucidating the development of PCa due to schistosomiasis infection.

Conclusion

This review of 20 publications of the co-existence of the MGS and PCa was not able to demonstrate a causal association of the two diseases. However, we were able to demonstrate the co-existence of PCa and schistosome eggs in the prostate indicating the need to investigate the contribution of the sequellae

of schistosomiasis infection with the development of PCa.

Recommendations

Based on the evidence of the co-existence of PCa and schistosomiasis eggs in the prostate, there is need to investigate the association of schistosomiasis infection to the aetiology or as a co-factor of PCa evolution especially in schistosome endemic areas. Examination of prostate tissues should be studied longitudinally and not only at the time at the time of treatment for prostate cancer in schistosomiasis endemic areas to determine the association of the two diseases. History of schistosomiasis infection should be taken into consideration to elucidate the evolution of schistosomiasis infection. Schistosomiasis associated prostatic cancer poses a diagnostic challenge especially if the disease is asymptomatic and relies on clinical outcomes. Thus, there is a need for appropriate diagnostic tools that can detect invasive conditions early and predict the possibility of PCa development. This might help initiate the management and treatment of such co-existing conditions especially in schistosomiasis endemic areas where schistosomiasis infections occur at very early ages whilst the severe effects of the disease might occur at older age.

Competing Interests

The authors declare that they have no competing interests.

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Contribution of Authors

ETC and TM did literature searches. ETC and TM did the analysis and reporting. ETC wrote the manuscript. MC, ENS and FM guided the process of the literature search and manuscript writing. MC and ENS has been involved in revising the manuscript critically for important intellectual content. All the authors read and approved the final of the manuscript.

References

1. World Health Organization. Neglected tropical diseases. WHO 2018; http://www.who.int/neglected_diseases/diseases/summary/en/ (accessed 2 Nov 2018).
2. Colley DC and Secor WE. Immunology of Human Schistosomiasis. Parasite Immunol. 2014; 36(8): 347–57.
3. McManus DP, Bergquist R, Cai P, Ranasinghe S, Tebeje BM and You H. Schistosomiasis-from immunopathology to vaccines. Semin Immunopathol. 2020; 42(3): 355–71.
4. Rollinson D. A wake up call for urinary schistosomiasis: reconciling research effort with public health importance. Parasitology 2009; 136(12): 1593–1610.
5. Elbaz T and Esmat G. Hepatic and Intestinal Schistosomiasis: Review. J Adv Res. 2001; 4(5): 445–52.
6. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ and Zhou XN. Schistosomiasis. Nat Rev Dis Primers. 2018; 4(1):13.
7. Gryseels B. Schistosomiasis. Infect Dis Clin North Am. 2012; 26(2): 3839–7.
8. World Health Organisation. Epidemiology table of schistosomiasis current estimated total number of individuals with morbidity and mortality due to Schistosomiasis *haematobium* and S. *mansoni* infection in Sub-Saharan Africa. WHO 2019; http://www.who.int/schistosomiasis/epidemiology/table/en/ (accessed 13 May 2019).
9. Utzinger J, Raso G, Brooker S, De Savigny D, Tanner M, Ornbjerg N, Singer BH and N'goran EK. Schistosomiasis and neglected tropical diseases:

towards integrated and sustainable control and a word of caution. Parasitol. 2009; 136(13): 1859–74.
10. Keating JH, Wilson RA and Skelly PJ. No overt cellular inflammation around intravascular schistosomes in vivo. J Parasitol. 2006; 92(6): 1365–9.
11. Mbabazi PS, Andan O, Fitzgerald DW, Chitsulo L, Engels D and Downs JA. Examining the relationship between urogenital schistosomiasis and HIV infection. PLOS Neg Trop D 2011;5: e1396.
12. Feldmeier H, Leutscher P, Poggensee G and Harms G. Male genital schistosomiasis and haemospermia. TM &IH. 1999; 4(12): 791–3.
13. Leutscher, PD, Pedersen M and Raharisolo C. Increased prevalence of leukocytes and elevated cytokine levels in semen from *Schistosoma haematobium*-infected individuals. J Infect Dis. 2005; 191(10): 1637–47
14. Manasseh AN, Echejoh GO, Tanko MN, Olugbenga O, Dakum SK and Mandong BM. Prostatic adenocarcinoma co-existing with schistosomiasis: A case report and review of literature. Inter J Med Sci. 2009; 1: 33–7.
15. Bustinduy AL and King CH. Schistosomiasis, chapter 49 in Farrar J, Hotez P, Junghanssv T, Lalloo D and White N. Manson's Tropical Diseases, 23rd ed., Elsevier, (in press).
16. Leutscher P, Ramarokoto CE, Reimert C, Feldmeier H, Esterre P and Vennervald BJ. Community-based study of genital schistosomiasis in men from Madagascar. Lancet 2000; 8: 358(9198): 117–8.
17. Perdichizzi A, Nicoletti F, La Vignera S, Barone N, D'Agata R, Vicari E and Calogero AEE. . Effects of tumour necrosis factor-alpha on human sperm motility and apoptosis. J Clin Immunol 2007; 27(2): 152–62.
18. Gleason DF and Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974; 111(1): 58–64.
19. Humphrey PA, Moch H, Cubilla AL, Ulbright TM and Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. EAU 2016; 70(1); 106–19.
20. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL and ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am. J. Surg. Pathol. 2005; 29:1228–42.
21. National Comprehensive Cancer Networks Organisation (NCCN). Guidelines for Patients:Prostate Cancer Version 1. NCCN 2016; http://www.NCCN.org/patients (accessed 10 April 2018).
22. Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2018. CA Cancer J Clin 2018; 68(1):7–30:
23. Prostate Cancer Foundation of Australia (PCFA). Understanding Prostate Cancer.PCFA 2014; http://www.pcfa.org.au (accessed 23 May 2018).
24. Zimbabwe National Cancer Registry (ZNCR). Profile of Cancer in Zimbabwe 2014. ZNCR 2015; http://www.zimcancerregistry.co.zw/cancer-profile-in-zimbabwe.html (accessed 19 May 2018).
25. Miah S and Catto J. Benign prostate hyperplasia and prostate cancer risk. Indian J Urol 2014; 30(2): 214–8.
26. Mottet N, Bastian PJ, Bastian J, Bellmunt, van def-Berg RCN, Bolla. M, van-Casteren NJ, Cornfor P, Jonian S, Mason MD, Matveer V, van-der Kwast TH, van-der-Poet, Rouviere O and Weigel T. Guidelines on prostate cancer. Euro. Urol 2015; https://uroweb.org/wp-content/uploads/1607-Prostate-Cancer_LRV3.pdf (accessed 25 May 2018).
27. Elfaki TEM, Kebayer MHA and Elsayid M. Association between urinary schistosomiasis and prostate cancer in Al-Shajara area Khartoum, Sudan. IJNRHN 2015; 2(3): 91–7.
28. PubMed Health. Behind the headlines health news from NHS choices. Frequent ejaculation may decrease prostate cancer. PubMed Health, 2017; https://www.ncbi.nlm.nih.gov/pubmedhealth/behindtheheadlines/news/2017-07-06-frequent-ejaculation-may-decrease-prostate-cancer-risk/. Posted Jul 2017 (accessed June 2018).
29. Bashir MN, Ahmad MR and Malik A. Risk factors of prostate cancer: A case- control study in Faisalabad, Pakistan. Asian Pac J cancer Prev 2014; 15(23): 10237–40.
30. Huncharek M, Haddock KS, Reid R and Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. Am J Public Health 2010; 100(4): 693–701.
31. Dennis LK and Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology 2002; 13(1): 72–9.
32. Hosseini M, SeyedAlinaghi S, Mahmoudi M and McFarland W. A case-control study of risk factors for prostate cancer in Iran. Acta Med Iran 2010; 48(1): 61–6.
33. Parent ME, Desy M and Siemiatycki J. Does exposure to agricultural chemicals increase the risk of prostate cancer among farmers? Mcgill J Med 2009; 12(1): 70–7.
34. Balkwill F and Mantovani A. Inflammation and cancer: Back to Virchow? Lancet 2001; 357(9255): 539–45.
35. Malik MO, Veress B, Daoud EH and El Hassan AM. Pattern of bladder cancer in the Sudan and its relation to schistosomiasis: A study of 255 vesical carcinomas. Am J Trop Med Hyg 1975; 78(10-11):219–26.
36. International Agency for Research on Cancer (IARC). *Schistosomas*, liver flukes and helicobacterpylori. IARC working group on the evaluation of carcinogenic risks to humans, Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum 2008; 61:1–241.
37. Sheweita SA, El-Shahat FG and Bazeed MA. Effects of *Schistosoma haematobium* infection on drug-metabolizing enzymes in human bladder cancer tissues. Cancer Lett. 2004; 205(1): 15–21.

38. Botelho MC, Soares R, Vale N, Ribeiro R, Camilo V, Almeida R, Medeiros R, Gomes P, Machado JC and da Costa JMC. *Schistosoma haematobium*: Identification of new estrogenic molecules with estradiol antagonistic activity and ability to inactivate estrogen receptor in mammalian cells. Exp Parasitol 2010; 126(4): 526–35.
39. Botelho MC, Alves H, Barros A, Rinaldi G, Brindley PJ and Sousa M. The role of estrogens and estrogen receptor signaling pathways in cancer and infertility: The case of schistosomes. Tre Par 2015; 31(6): 246–50.
40. Botelho MC, Alves H and Richter J. Estrogen catechols detection as biomarkers in schistosomiasis induced cancer and infertility. Letters in Drug Design & Discovery 2016; 13(2):1–4.
41. Rosin MP, Saad el Din Zaki S, Ward AJ and Anwar WA. Involvement of inflammatory reactions and elevated cell proliferation in the development of bladder cancer in schistosomiasis patients. Mutat Res 1994; 305(2): 283–92.
42. Salim E, Morimura K, Menesi A, El-Lity M, Fukushima S and Wanibuchi H. Elevated oxidative stress and DNA damage and repair levels in urinary bladder carcinomas associated with schistosomiasis. Int J Cancer, 2008;123(3): 601–8.
43. International Agency for Research on Cancer (IARC). Working Group on the Evaluation of Carcinogenic Risks to Humans, Biological agents, "A review of human carcinogen," IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012; 100: 1–44. Available at https://monographs.iarc.fr/wp-content/uploads/2018/08/14-002.pdf (accessed 12 February 2018).
44. Al Adnani MS. Schistosomiasis, metaplasia and squamous cell carcinoma of the prostate: Histogenesis of the squamous cancer cells determined by localization of specific markers. Neoplasma1985; 32: 613–22.
45. Alexis R and Domingo J. Schistosomiasis and ad enocarcinoma of prostate: A morphologic study. Hum Pathol 1986; 17(7): 757–60.
46. Tungekar MF and Al Adnani MS. Sarcomas of the bladder and prostate: The role of immunohistochemistry and ultrastructure in diagnosis. Eur Urol 1986; 12(3): 180–3.
47. Godec CJ, Grunberger I and Carr GA. Simultaneous presence of schistosomiasis and advanced cancer in prostate. J Urol 1992; 39(6): 547–9.
48. Ma TK, and Srigley JR. Adenocarcinoma of prostate and schistosomiasis: A rare association. Histopathol 1995; 27(2): 187–9.
49. Cohen RJ, Edgar SG and Cooper K. Schistosomiasis and prostate cancer. Path 1995; 27(2):115–6.
50. Basilio-de-Oliveira CA, Aquino A, Simon EF and Eyer-Silva WA. Concomitant prostatic schistosomiasis and adenocarcinoma: Case report and review. Braz. J Infect Dis 2002; 6(1): 45–9.
51. Bacelar A, Castro LG, De Queiroz AC and Cafe E. Association between prostate cancer and schistosomiasis in young patients: A case report and literature review. Braz J Infect Dis 2007; 11(5): 520–22.
52. Mazigo HD, Zinga M, Heukelbach J and Rambau P. Case series of adenocarcinoma of the prostate associated with *Schistosoma haematobium* infection in Tanzania. J Glob Infect Dis 2010; 2(3): 307–9.
53. Figueiredo JC, Richter J, Borja N, Balaca A, Costa S, Belo S and Grácio MA. Prostate adenocarcinoma associated with prostatic infection due to *Schistosoma haematobium*: Case report and systematic review. Parasitol Res 2015; 114(2): 351–8.
54. El-Hawary AK and Foda AAM. Incidentally detected schistosomiasis in male genital organs: Case reports and review of literature. Am J Cas Rep 2016; 4(1): 25–30.
55. Metrogos V, Ramos N, Marialva C and Bastos J. Rare association between prostate adenocarcinoma and schistosomiasis: A case report. ACTA Urológica Portuguesa 2017; 34(3-4): 41–3.
56. Peiffer LB, Poynton SL, Ernst SE, Hicks JL, De Marzo AM and Sfanos KS. Inflammation-associated pathologies in a case of prostate schistosomiasis: Implications for a causal role in prostate carcinogenesis. Prostate 2019; 79(11): 1316–25.
57. Mukendi AM, Doherty S and Ngobese L. Schistosomiasis on prostate biopsy, adenocarcinoma on transurethral resection of prostate specimens. Journal of Clinical Urology 2019: p. 2051415819889203.
58. Lodhia J, Mremi A, Pyuz JJ, Bartholomeo N and Herman AM. Schistosomiasis and cancer: Experience from a zonal hospital in Tanzania and opportunities for prevention. Journal of Surgical Case Reports. 2020; 5(44): 1–5.
59. Shamma AH. Schistosomiasis and Cancer in Iraq. Am J Clin Pathol 1955; 25(11): 1283–4.
60. Mutengo MM, Mudenda V, Mwansa JC, Kaonga K, Sianongo S, Wamulume, HI and Shinondo, CJ. Presence of schistosomiasis in genital biopsies from patients at the University Teaching Hospital in Lusaka, Zambia. Med J Zambia 2009; 36(3): 114–18.
61. Okani C, Akang E and Ogunbiyi O. Incidence of sub-clinical prostatic disease at autopsy in the University college hospital, Ibadan. Open Access J. Urol. 2013; 3(2): 80–6.
62. Der EM, Quayson SE, Mensah JE and Tettey Y. Tissue schistosomiasis in Accra Ghana: A retrospective histopathologic review at the Korle-Bu Teaching Hospital (2004–2011). Pathol Discov 2015; 3(1): 1–6.
63. Ehsani L and Adeboye OO. Schistosomiasis of the prostate: A case report. Anal Quant Cytol Histol 2013; 35(3): 178–80.
64. Bonnefond S, Cnops L, Duvignaud A, Bottieau E, Pistone T, Clerinx J and Malvy D. Early complicated schistosomiasis in a returning traveller: key

contribution of new molecular diagnostic methods [case report]. Inter J Infect Dis 2019;79: 72–4.
65. Faust EC. An inquiry into the ectopic lesions in schistosomiasis. Am. J.Trop. Med & Hyg 1948; s1-28:175–99.
66. Patil PS and Elem B. Schistosomiasis of the Prostate and the Seminal Vesicles: Observations in Zambia. J Trop Med Hyg 1988; 91(5): 245–58.
67. Gelfand M, Ross CMD and Blair DM. Schistosomiasis of the male pelvic organs: Severity of infection as determined by digestion of tissue and histologic methods in 300 Cadavers. Am J Trop Med Hyg 1970; 19(5): 779–84.
68. Sharma R, Mahore SD, Kolhe H, Patil R, Bathale K and Wilkinson A. *Schistosoma* in the prostate: A case report. Int J of Allied Med Sci and Clin Research 2015; 3(3): 293–97.
69. Gomez EC, Domingues ALC, de-Aguiar Júnior FCA, dos Santos KRP, Rehn VNC, de Melo Lira MM and Barbosa CS. First record of prostatic schistosomiasis in Pernambuco, Brazil: signs of chronicity in an endemic disease. Rev Patol Trop 2016; 45: 132–8.
70. Yu Z, Wei C, Wang Y, Ye Z, Wang Z, Chen Z, Ni L, Yang S, Gui Y, Guan Z, Cai Z and Lai Y. Prostatic *Schistosoma japonicum* with atypical immunophenotyping of individual glandular tubes: A case report and review of the literature. Southeast Asian J Trop Med Public Health 2013; 44(4): 568–73.
71. El-Bolkany MN, Mokhter NM, Ghonem MA and Hussein MH. The impact of schistosomiasis on the pathology of bladder carcinoma. Cancer 1981; 48(12): 2643–8.
72. Tuffour I, Ayi I, Gwira TM, Dumashie E , Ashong Y and Appiah-Opong R. *Schistosoma* egg antigen induces oncogenic alterations in human prostate cells. Analytical Cellular Pathology 2018:(1-2)–10.
73. Midzi N, Mduluza T, Mudenge B, Foldager L and Leutscher PDC. Decrease in seminal HIV-1 RNA load after praziquantel treatment of urogenital schistosomiasis coinfection in HIV-positive men—an observational study. Open Forum Infect Dis 2017; 4(4): ofx199.
74. Leutscher PD, Host E and Reimert CM. Semen quality in *Schistosoma haematobium* infected men in Madagascar. Acta Trop 2009; 109(1): 41–4.
75. Kjetland EF, Ndhlovu, PD, Gomo E, Mduluza T, Midzi N, Gwanzura L, Mason PR, Sandvik L, Friis H and Gundersen SG. Association between genital schistosomiasis and HIV in rural Zimbabwean women. AIDS 2006; 20(4): 593–600.
76. Stecher CW, Kallestrup P, Kjetland EF, Vennervald B and Petersen E. Considering treatment of male genital schistosomiasis as a tool for future HIV prevention: A systematic review. Int J Public Health 2015; 60(7): 839–48.
77. Kayuni S, Lampiao F, Makaula P, Juziwelo L, Lacourse JE, Reinhard-Rupp J, Leutscher PDC and J. Stothard R. Systematic review with epidemiological update of male genital schistosomiasis (MGS): A call for integrated case management across the health system in sub-Saharan Africa. Parasite Epidemiol Control 2018:3:e00077.