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Review Article

Time-Trend Analysis of Bladder Cancer and its Association with Bilhariziasis in Egypt

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ABSTRACT

Background: Both bladder cancer and schistosomiasis are endemic in Egypt. The former has a unique epidemiological pattern, which has been linked to bladder infestation by Schistosoma. The last decades have witnessed a great reduction in the infection rate of schistosomiasis and a decline in the incidence and changes in the patterns of bladder cancer. Whether these changes are linked to each other or a co-incidence is a subject of investigations.
Subjects and Methods: Literature on epidemiological data of bladder cancer and Schistosoma in Egypt was searched for in Medline, Scopus, PubMed, and Google Scholar. Furthermore, a hand search for literature and reports released by the Egyptian government and involved agencies was performed.
Results: Studies describe an overall reduction in Schistosoma infection rate from 80% in 1920s to 1.2% in 2006. Studies on bladder cancer epidemiology, on the other hand, agree on a decline in incidence and changes in the pattern, but differ in figures describing the magnitude of these changes. Many studies tried to ling the changes in Schistosoma and bladder cancer patterns. The evidence for this link, however, seems to be insufficient for a cause-and-effect relationship.
Conclusion: The relationship between the reduction in schistosomiasis infection rate and the changes in bladder-cancer epidemiological pattern in Egypt cannot be overlooked, but needs to be proved by more reliable evidence like prospective studies that include local health facilities and tertiary cancer centers.
Objective: explore the possible cause-and-effect relationship between the changes in Schistosoma infection rates and incidence and patterns of bladder cancer in Egypt.

Introduction

Bladder cancer

Although bladder cancer is considered the ninth most common cancer all over the world, its incidence differs greatly across different countries in the world. It is generally more prevalent in the developed compared to developing countries, however, some areas are considered exceptions (1). The Middle East, Egypt, Iraq, and southern parts of Saudi Arabia, have relatively high incidence rates (2, 3). Bladder cancer is considered the most common solid tumor in Egyptian men and second only to breast cancer in Egyptian women (4), and has been well known for years to be the most common cause of death of young men in Egypt (5). While the overall incidence of bladder cancer is comparable between the United States and Egypt (13.1and11.6 per 100,000 persons respectively) (6), its mortality rate is 4 times greater in Egyptians than Americans (16.3% and 3.7% respectively) (7). This is considered the highest bladder cancer mortality rate in the world (8, 9).

Transitional cell carcinoma (TCC) and squamous cell carcinoma (SCC) are the most common histopathological types of bladder cancer. The risk factors linked to each type are different. Historically, Ferguson was the first to connect bladder infestation with Schistosoma to SCC (10). His work formed the basis of most investigations that took place over the proceeding century and focused on finding the exact mechanism of carcinogenesis or a cause-and-effect relationship. The major risk factors reported for TCC are smoking and occupational/environmental exposure to some toxins and heavy metals (11).

Bilharziasis

Schistosoma, the parasite infests humans causing the triad of hematuria, dysuria, and anemia, was first described by a German physician named Theodor Bilharz in 1850. Hence, the names Schistosomiasis and Bilharziasis are interchangeable.

Having the freshwater snail (Bulinus species) as an intermediate host essential for their life cycle, these worms predominate in watershed lands and farms irrigated from rivers (Nile in Egypt). Changes affecting rivers whether natural as floods or man-made like building dams or irrigation channels will affect the snail population and eventually the prevalence of schistosomiasis. Many studies showed that building the Aswan High Dam in Egypt (1960-1970) has resulted in a dramatic increase in the snail population and incidence of the disease peaked by 10-fold (2).

Schistosomal bladder-cancer

Bilharzia-associated bladder cancer has a unique epidemiologic pattern in terms of age at diagnosis, gender distribution, histopathological type, stage of the disease at j programs have succeeded to reduce the prevalence of Schistosomiasis from 70-80% in early the 1920s to as low as 1.2% in 2006 (2). This reduction in the rate of Schistosomal infestation was paralleled by an increase in the exposure to TCC risk factors, specifically smoking and occupational toxins (12).

Reports on bladder cancer in Egypt show an obvious change in its epidemiologic pattern over the last decades and most of these reports attribute that change to the good control of Schistosomiasis achieved (1, 2, 4, 7, 13, 14). The aim of this literature review is to explore the changes in bladder-cancer epidemiological patterns and their relationship to the changes in Schistosoma infestation rates. Furthermore, the possible scientific clarification for these changes and associations will be discussed.

Subjects and Methods

A literature search using “bladder cancer”, “epidemiology”, “schistosomiasis”, and “bilharziasis” subject headings was conducted. PubMed, Medline, Scopus, and Google Scholar databases were searched. The search was limited to “Egypt” and “English” language. Due to limited resources found, the search was then expanded using the references and bibliographies of the useful literature found in the first search. A general internet search was made looking for reports and literature related to the epidemiology and control of bilharzia released or published by the Egyptian government and national and international non-governmental organizations and agencies. A specific search was made for the world health organization (WHO) and World Bank (WB) reports on bilharzia in Egypt. The results were then filtered to include only the studies that investigated the epidemiological aspects of bladder cancer and bilharzia. The literature was later grouped according to following factors: the time period covered, the number of patients’ records analyzed, the place of the study, and the epidemiological parameters studied. Results of the selected studies were then summarized and analyzed.

Results

Schistosomiasis:

The disease control efforts made by the Egyptian government and the international agencies were directed into three parallel lines: snail control, chemical Schistosomal control, and public education. However, the incidence of Bilhariziasis in the rural areas was as high as 50% by the middle of the last century (15). The main breakthrough in the disease control history was the availability of praziquantel, a chemical agent with more than 90% effectiveness against the worms and negligible side effects (16). In conclusion, the local and international programs to control the disease were highly successful, with a reduction in its prevalence from around 40% in 1980 to barely above 1% in 2006 (17).

Bladder cancer:

The incidence of bladder cancer over the world has changed greatly during the last few decades. According to the International Agency for Research on Cancer 2012 figures, Belgium has the highest rate of bladder cancer (17.5/100,00 persons) followed by Lebanon and Malta, while Egypt ranked 10th with incidence rate of 13.1/100,000 persons (6). Egypt, however, continued to have the highest bladder cancer mortality rate in the world (8, 9, 18). Indeed, the incidence and mortality rates are not the only differences between bladder cancer in Egypt and other parts of the world. It has been well established many decades ago that bladder cancer in Egypt has a unique epidemiologic pattern(19). In comparison with the western countries, bladder-cancer patients in Egypt are younger (mean age is 47 years compared to 72.9 in USA), and with more profound male predominance (male to female ration of 7.8:1 compared to 3.5:1 in USA)(2, 5, 20). Pathologically, the SCC type (76.6%) dominates bladder cancer in Egypt. It is of a higher stage at presentation and poorer prognosis (5, 20, 21). Schistosoma has been thought to be the cause for both the high incidence of bladder cancer in Egypt as well as its unique pattern (19). Physical (chronic irritation), chemical (production of carcinogens such as N-nitrosamines) and microbiological (associated bacterial infection) mechanisms for schistosoma-induced bladder cancer have been hypothesized and investigated thoroughly (10, 22-25).

There are many other proved and potential risk factors for bladder carcinoma; these include smoking (tobacco, water pipe, and shisha), occupational toxins and chemicals (aromatic amines), environmental exposure to heavy metals (arsenic in drinking water), use of artificial sweeteners (saccharin and cyclamates), and medications like cyclophosphamide and chlornaphazine(11, 12). These risk factors, however, have been linked mainly to TCC (11, 26).

Changing epidemiological trends:

The changes in bladder-cancer epidemiology, and their hypothesized relationship to similar changes in the epidemiology of

schistosomiasis, have been addressed in several studies. Most of the literature found during the search for this review were retrospective studies and relied on data obtained mainly from the national cancer institute in Cairo (NCI). All the studies reviewed in this work agree on the changes in the major epidemiologic parameters of bladder cancer in Egypt. They showed a significant decline in the relative frequency of bladder cancer in Egypt. This was also evident in the 2012 world cancer incidence and mortality report (6). It clearly indicated a rise in the mean age of patients, a reduction in the male to female ratio, an obvious domination of TCC over SCC in the last years, and a significant drop in the number of patients with bilharzial-egg positivity (1, 4, 5, 7, 12-14, 27). The longest time period covered and the largest number of patients' records included were found in the study conducted by Gouda et al. in 2007 (4). They analyzed the records of 9843 patients diagnosed and treated over 38 years (1970 through 2007) in NCI. The next study in the time length and patient's number is that of Zaghloul et al. who were able to cover the period from 1988 to 2004, and collected 5071 records (14). The NCI records were their main data source as well. The main drawback of this study, however, was its limitation to patients treated with cystectomy. The characteristics of the four major studies are summarized in table 1.

Table 1: The four major studies tracing bladder carcinoma and schistosomaSchistosoma trends

Study	Patients number	Time covered	Value of epidemiologic parameters at start and end of the study period					
			RF %	Age (yr)	M:F	SCC %	TCC %	BEP% (Bilharzi Egg Positive))
Gouda et al. (2007*	9843	1970-2007	27.6 to 11.7	47.4 to 60.5	5.4:1 to 3.3:1	75.9 to 28.4	16 to 65.8	82.4 to 55.2
Zaghloul et al. (2008**	5071	1988-2004		51 to 57.2	3.2:1 to 3.6:1	56.9 to 43.6	33.3 to 47.7	62.3 to 54.6
Felix et al. (2008¥	2778	1980-2005		46.5 to 60	3.3:1 to 4.2:1	78 to 27	21 to 72.7	49.6 to 46.6
Salem et al. (201π	1932	2001-2010	18 To 13	41 to 52	6.5:1 to 4.2:1	73 to 25	20 to 66	80 to 50

*National Cancer Institute (NCI)only
** cystectomy patients form NCI only
¥ data from NCI, Gharbia cancer center in the north, and Minia cancer center in the south
π Kasr Al-Aini hospital/cairo

El-Bolkainly et al. (1981) and Koraitim et al. (1995) tried in their studies to find the epidemiological differences between bilharzial-egg positive (BEP) and negative (BEN) bladder cancer patients (5, 27). El-Bolkainy and his group studied 1095 cystectomy patients records from NCI and Al-Mansoura center in the period from 1976 to 1978. Koraitim, on the other hand, compared patients from two different time periods (1962-1967, and 1987-1992) in a different location (Alexandria). Despite these differences, the two groups reached similar conclusions. They found that the BEP patients had a significantly lower mean age, a more domination of males over females, and were more likely to have SCC.

Fedewa et al. (2009) failed to show any significant change in the epidemiological parameters in their study, which included 1209 patients from the Gharbia region during 1999 through 2002(1).
Less attention was paid to the pathological stage and grade of bladder cancer in the studies addressing the epidemiology of the disease despite its important clinical implications. Although no significant association was found between the BEP status and tumor stage, grade, and lymph node involvement status, a shift from solid nodular tumors towards papillary tumors was noticed, with higher grades tending to be found in BEN cases (1, 5).

Regarding the prevalence of schistosomiasis, the early efforts to control the disease using antimony compounds and molluscicides had a very limited success. There was a reduction in its prevalence from around 80% in 1920 to a slightly more than 50% in 1980. The adoption of Schistosoma Research Project (SRP) by the National Schistosoma Control Program and the mass treatment with praziquantel, however, has succeeded to drop the prevalence to 6.6% by 1993 and 1.2% by 2006 (Fig.1)(17). In addition to schistosoma eradication programs, many factors dramatically affected the incidence and prevalence of schistosoma in the Egyptian population. Two important factors to mention here are the changes that the introduction of an irrigation system triggered after the completion of the Aswan High Dam in the mid-1900s, and climate changes, specifically the recorded rise in temperature and its effect on the schistosomal intermediate host (the Bullinus snail) (28).

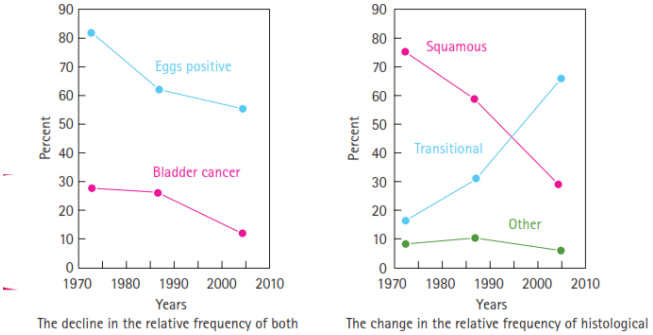

Figure 1*: Relative frequency of bladder cancer and bilharziasis in Egypt over a 37 years period. Courtesy of the Journal of the National Cancer Institute (17).*

Discussion

A change in the epidemiological pattern of bladder cancer in Egypt is clear and obvious. This change appears to be linked to the successful control of schistosomiasis. Epidemiologic data form the basis for this conclusion. These epidemiologic studies were successful in covering almost all parts of the country and including a large number of records. Epidemiologic data alone, however, are not sufficient for a cause-and-effect relationship. Some of these epidemiological changes have been noticed also in many other

countries, for example the overall reduction in bladder cancer relative frequency and relative risk, as well as the increased mean age of the patients (6). There is great reduction in the relative frequency of bladder cancer in Egypt over the past few decades. The decrease from more than 45% to around 13% cannot be considered parallel to the magnitude of reduction in the prevalence of schistosomal infestation from 80% to 1.2%, which was achieved as early as 2006. The increased exposure to other risk factors for bladder carcinoma should not be overlooked. Smoking habit is increasing among the Egyptian population, in particular the non-classical types of smoking like water-pipe smoking (shisha).

Moreover, all the studies that were included in this search were conducted in the NCI or one of the major cancer institutes of Egypt. Therefore, these studies are analyzing the same data set. An important point to take in account is that bladder-cancer patients are usually managed at the local health-facility level and transferred to a tertiary center only after failure of early conservative therapeutic modules and a need for more invasive treatment emerges. In addition, some studies analyzed only records of patients who underwent cystectomy.

The degree of bilharzial infestation needs to be taken in consideration. The carcinogenic effect of schistosoma is related to the degree of irritation of the bladder mucosa, thus mildly infested and non-infested bladders may react similarly when exposed to another risk factor like smoking.

In such patients, TCC would be the expected histopathological type since it develops in the normal transitional mucosa of the bladder. For SCC to develop, it requires severe irritation of the bladder mucosa causing a squamous metaplasia, which is followed later by dysplastic changes. Another weakness in the present studies is that they overlooked the pathological stage and grade of the tumor and their time trends. SCC is known to be locally advanced but rarely metastasizes because of the severe fibrosis of the perivesical lymphatic channels caused by schistosomal infestation and irritation.

Based on the above, and to uncover the exact magnitude of the epidemiological changes of bladder cancer in Egypt and its relationship to the control of schistosomiasis, a more systematic and nationwide study is required that includes the local health facilities in addition to the tertiary and referral centers. A prospective study would be more likely to reflect the reality, but more difficult to conduct.

Conclusion

This review has demonstrated that there is some evidence supporting the hypothesis linking the changes in the epidemiological pattern of bladder cancer in Egypt to similar and parallel changes in the epidemiology of schistosomiasis. However, this evidence alone is not sufficient to infer a solid conclusion on a cause-and-effect relationship between the reduction in the incidence of schistosomiasis and the pattern changes of bladder cancer.

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