Author Manuscript Published OnlineFirst on December 6, 2011; DOI: 10.1158/1055-9965.EPI-11-0589
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Urinary bladder cancer risk factors in Egypt: a multi-center case-control study

Yun-Ling Zheng[1], Sania Amr[2], Doa'a A.Saleh[3], Chiranjeev Dash[1], Sameera Ezzat[4], Nabiel N. Mikhail[5], Iman Gouda[6], Iman Loay[6], Tamer Hifnawy[7], Mohamed Abdel-Hamid[8], Hussein Khaled[6], Beverly Wolpert[2], Mohamed A. Abdel-Aziz[5], and Christopher A. Loffredo[1].

[1]Carcinogenesis, Biomarkers and Epidemiology Program, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA, [2]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore MD, USA, [3]Department of Community Medicine, Cairo University, Cairo Egypt, [4]National Liver Institute, Menoufiya University, Egypt, [5]South Egypt Cancer Institute, Assiut University, Egypt, [6]National Cancer Institute, Cairo, Egypt, [7]Department of Public Health, Beni Suif University, Egypt, [8]Department of Microbiology, Minia University and National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt.

Running title: Urinary bladder cancer risk factors in Egypt

Correspondence Author: Christopher A. Loffredo Ph.D., Lombardi Comprehensive Cancer Center, Georgetown University, 3800 Reservoir Road, NW, LL Room 153, Washington DC, 20057-1465, Tel: (202) 687-3758 Fax: (202)784-3034, E-mail: cal9@georgetown.edu

Keywords: bladder cancer; UC, SCC, risk factors, cigarette smoking, waterpipe smoking, schistosomiasis, gender differences, Environmental Tobacco Smoke.

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ABSTRACT

Background: We investigated associations between tobacco exposure, history of schistosomiasis and bladder cancer risk in Egypt.

Methods: We analyzed data from a case-control study (1,886 newly diagnosed and histologically confirmed cases and 2,716 age-, gender-, and residence-matched, population-based controls). Using logistic regression we estimated the covariate-adjusted odds ratios (OR) and 95% confidence interval (CI) of the associations.

Results: Among men, cigarette smoking was associated with an increased risk of urothelial carcinoma (UC) (OR = 1.8, 95% CI = 1.4, 2.2), but not squamous cell carcinoma (SCC); smoking both waterpipes and cigarettes was associated with an even greater risk for UC (OR = 2.9, 95% CI = 2.1, 3.9) and a statistically significant risk for SCC (OR = 1.8, 95% CI = 1.2, 2.6). Among non-smoking men and women, to environmental tobacco smoke exposure was associated with an increased risk of UC. History of schistosomiasis was associated with increased risk of both UC (OR = 1.9, 95% CI = 1.2, 2.9) and SCC (OR = 1.9, 95% CI = 1.2, 3.0) in women and to a lesser extent (OR = 1.4, 95% CI = 1.2, 1.7 and OR = 1.4, 95% CI = 1.1, 1.7, for UC and SCC respectively) in men.

Conclusions: The results suggest that schistosomiasis and tobacco smoking increase the risk of both SCC and UC.

Impact: This study provides new evidence for associations between bladder cancer subtypes and schistosomiasis, and suggests that smoking both cigarettes and waterpipes increases the risk for SCC and UC in Egyptian men.

INTRODUCTION

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The two predominant histological types of urinary bladder cancer are urothelial cell and squamous cell carcinoma (UC and SCC, respectively). Cigarette smoking, occupational exposures to carcinogens, and chronic infection with *Schistosoma haematobium* (SH) have been established as risk factors for bladder cancer (1-6). In industrialized countries, UC accounts for 90% of the cases, and occurs mainly after the age of 60 years. Elsewhere, chronic schistosomiasis has been associated with SCC, which occurs at younger ages (7-9).

In the past in Egypt, where SH was endemic, bladder cancer diagnoses were made at younger ages (<50 y) than in developed countries, and 68% of the cases were identified histologically as SCC (10-12). With the government's efforts to eradicate SH and treat infected individuals over the past three decades, a shift from SCC to UC and an increase in the mean age at diagnosis have been reported (1;13). However, the incidence of bladder cancer in Egypt has not decreased; this malignancy remains the most commonly diagnosed in men (14-16). Furthermore, the female-to-male ratio of 1:4 to 1:7 noted in the 1980s (13) was almost unchanged in 2008 (1;14;16). Tobacco smoking, a well established risk factor for bladder cancer, could explain its persisting high incidence in men; however, it falls short in explaining why bladder cancer among women has not decreased, because in Egypt, 22 to 47% of adult men, but only 2 to7 % of adult women reported smoking in recent surveys (17-19), and historically smoking was even less prevalent among women than it is currently. An additional unique feature of tobacco consumption in Egypt, compared to other regions, is the high prevalence of waterpipe smoking (18;20). Furthermore, environmental tobacco smoke (ETS), although established as lung carcinogen (IARC), has not been established as a risk factor for bladder cancer.

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To date, epidemiological investigations of bladder cancer in Egypt have been small studies focused on men (21;22) from a specific geographical area or a specialty clinic, such as a recent report assessing 26 years of bladder cancer pathology data from the National Cancer Institute (NCI) in Cairo (1). To address these gaps, we are conducting a multi-center case-control study to investigate different risk factors potentially associated with this malignancy. In this report, we examine the associations between cigarette and waterpipe smoking, ETS exposure, SH infection, and bladder cancer risk, in men and women, separately.

MATERIALS AND METHODS

The Institutional Review Boards of the three collaborating cancer centers in Egypt (the National Cancer Institute in Cairo, the Minia Oncology Center in Minia, and the South Egypt Cancer Institute in Assiut), the University of Maryland at Baltimore, Georgetown University, and the National Scientific and Research Ethical Committee at the Egyptian Ministry of Health and Population approved this study. A signed or witnessed informed consent was obtained from each study participant.

Study population:

Bladder cancer cases were recruited from the three referral cancer centers in Egypt listed above. These institutions serve the Cairo metropolitan area and surrounding regions in northern Egypt, and the upper and lower region of southern Egypt, respectively. They are the sole tertiary care centers for bladder cancer in their regions. Eligible cases were adults between the ages of 19

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and 80, self-identified as able to participate in an interview, and diagnosed within 12 months with presumed bladder cancer. Patients who had a prior history of other cancers were excluded. For each case, the pathology report and available slides prepared from the surgical or biopsy specimen of urinary bladder tissue were reviewed by either one of the two study pathologists (I.G. and I.L.) who worked together to standardize case classification, and report it as: 1) UC; 2) SCC; 3) adenocarcinoma; or 4) other, including undifferentiated carcinomas. Carcinoma that metastasized to the bladder was excluded. This report includes only UC and SCC cases.

Non-cancer controls were randomly selected from the general population to frequency-match the cumulative group of cases on gender, age (5-year interval), governorate (province) of current residence, and urban/rural place of residence. Two methods were used to recruit controls: (i) random sampling of households; and (ii) random sampling of family health records. For each governorate, the number of required controls and their characteristics (age and gender) were determined by the number of cases who were already recruited and who resided in that governorate, as follows.

(i) Random sampling of households: On a given day, the study recruiters visited the selected village. For each designated village, a street was randomly selected and a systematic random sampling method was applied to approach residents on both sides of the street. If none of the house occupants matched the required gender and age-range controls, the recruitment team moved to the next house. Once a potentially eligible participant was identified in a household, the trained interviewer explained the study to the prospective subject and offered participation.

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(ii) Random sampling of family health records: In Egypt, most administrative districts (neighborhood or village within the governorate) have a government-subsidized medical unit where residents receive healthcare, and each family living in that district has a medical record. With the permission of the National Regulatory authorities at the Egyptian Ministry of Health, we used these primary care health units as our sampling frame to randomly select healthy controls in the districts. The study recruiters visited the health units and used a systematic random sampling method to examine the family health records for a potential matched control. Then the recruiter approached the prospective participants at home, explained the study, and offered participation.

Regardless of the sampling methodology, all controls fulfilled the following eligibility criteria: (1) no known diagnosis of any cancer; (2) between ages 19 and 80; and (3) self-identified as able to participate in an interview. Using a portable ultrasound machine, the physician accompanying the recruitment team performed an abdominal ultrasound examination to rule out any asymptomatic abdominal mass. The interview and phlebotomy were performed at the participants' home.

After explaining the study and obtaining the consent, trained interviewers administered to both cases and controls a structured questionnaire, assessing socio-demographic characteristics including current residence and birth governorate, prior medical history with emphasis on schistosomiasis or other urinary tract infection (UTI), cigarette and waterpipe smoking status and history, and reproductive history (for women). Histories of exposure to environmental tobacco smoke (ETS) at home and outside the home were also recorded.

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Variable definition and statistical analysis:

The primary exposures of interest were tobacco use, SH infection, and exposure to ETS. Less than 5% of the women in the study reported using any form of tobacco; therefore tobacco use was only analyzed in men. Tobacco use was categorized as "never users", "waterpipe only", "cigarette only", and "both waterpipe and cigarette". Participants who had smoked less than 100 cigarettes in their lifetime and had never smoked a waterpipe were classified as "never users"; those who smoked less than 100 cigarettes in their lifetime but reported smoking waterpipes were classified as "waterpipe only" users, "cigarette only" users were those who had never smoked waterpipes but had smoked at least 100 cigarettes in their lifetime, and "both waterpipe and cigarette" users were those reported smoking at least 100 cigarettes in their lifetime and also used waterpipes. We further explored the association of cigarette smoking with bladder cancer risk using the following variables: i) cigarette smoking status, categorized as "never", "former"(quit smoking at least one year prior to diagnosis), and "current" smokers; ii) cigarette smoking duration; iii) cigarettes smoked per day; iv) pack years of cigarette smoked. Smoking duration, number of cigarette smoked per day, and pack years of cigarette smoked were divided into quartiles based on distribution among controls, with the referent group being "never users". Risk of bladder cancer with waterpipe use was explored by creating variables similar to those created for cigarette smoking. The tobacco load that is placed on the holder of the waterpipe is called a "hagar". We used two variables to represent the dose of waterpipe smoking. Number of hagars smoked per day was created by multiplying the number of hagars smoked per smoking session with the reported number of sessions per day. "Hagar-

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years", a variable similar to the concept of "pack-years", was defined as the product of the number of hagars smoked per day and the number of years of waterpipe smoking. History of schistosomiasis was based on self-report. Participants who reported having been told about a diagnosis of schistosomiasis by their doctors, or who reported taking medications specific for schistosomiasis were classified as having a positive history of the disease. ETS exposure was categorized as: no exposure, exposed at home only, exposed outside home only, and exposed both at home and outside home.

Student t-test and chi-square tests were respectively used to compare continuous variables and categorical variables between cases and controls. We used unconditional logistic regression to assess the risk of bladder cancer with the primary exposures of interest. The analyses were stratified by gender to evaluate the gender differences in distributions of these risk factors and in the strength of the associations. The risk factors were also assessed separately for UC and SCC histological subtypes. All models were adjusted for the matching factors – age (categorized in 5-year intervals) and governorate of residence. In addition, multivariate models were adjusted for urban/rural residence, education (none, literacy classes/primary school, preparatory/high/technical school, or college/university), urinary tract infections other than schistosomiasis (yes/no), menopause status (women only), history of schistosomiasis or tobacco use (when appropriate). The covariates were selected *a priori* based on their known association with bladder cancer in this population. Two-way interactions of schistosomiasis with cigarette smoking, and waterpipe smoking were assessed by including the relevant product terms in the logistic model. *P*-values were two-sided and considered statistically significant if $P < 0.05$. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

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RESULTS

Characteristics of the study population:

From July, 2006 through July, 2010, a total of 4,049 presumed bladder cancer patients were approached at the three cancer centers, of whom 3,427 were eligible and 2,891 (84%) agreed to participate in our study. The study pathologists have completed a review of 2,134 cases to date, and 1,988 of them have been confirmed as primary bladder cancer. The remaining 146 (6.8%) were found to have non-malignancies or tumors that originated from other sites, and hence were excluded from the study. Among 757 cases awaiting confirmation, the distribution of age, gender, and prevalence of schistosomiasis were not statistically different from confirmed cases. In men the prevalence of tobacco smoking is not significantly different between confirmed cases and cases waiting to be confirmed. Among the confirmed cases, there were 689 SCC (35%), 1,197 UC (60%), and 102 other type primary bladder cancers (5%). For this report, we focused on SCC and UC. As of August, 2010, 2,792 eligible controls were approached and 2,716 (97%) agreed to participate. Of the 2,716 enrolled controls, 285 (10%) were recruited using random sampling of family health records and 2,431 (90%) were recruited using random sampling of households.

Table 1 presents the characteristics of study population. The vast majority of men (92.0% of cases and 79% of controls) and women (97.0% of cases and 92% of controls) had primary school or lower educational level attainment. There was a significantly higher percentage of male

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controls who reported completing secondary school or higher education. Among men, 95% of cases and 93% of controls were married, while among women, only 60% of cases and 63% of controls were married. Among the cases, the ratio of women to men was 1:6, 1:3 and 1:5 for UC, SCC and all cases, respectively. The mean ages for SCC were significantly younger than that for UC ($p < 0.01$).

Cigarette smoking and bladder cancer risk:

Among men, the prevalence of cigarettes smoking was 77% for UC cases, 69% for SCC cases, and 65% for controls, as shown in Table 2. Those who reported ever smoking cigarettes, but not waterpipes, had a significant association with increased risk of UC, with an adjusted odds ratio (OR) of 1.8 (95% CI = 1.4 to 2.2). This behavior was not significantly associated with an increased risk of SCC. Importantly, smokers who smoked both cigarettes and waterpipe had a significantly elevated risk of both UC and SCC, with an OR of 2.9 (2.1 to 3.9) and 1.8 (1.2 to 2.6) for UC and SCC, respectively (Table 2). Among the cigarette smokers, current smokers had significantly elevated risk of UC, with an OR of 2.0 (95% CI = 1.6 to 2.5, Table 3). Significant dose-response relationships between the number of cigarettes smoked per day and risk of UC ($P_{trend} < 0.01$), between years smoked and risk of UC ($P_{trend} < 0.01$), and between pack-years and risk of UC ($P_{trend} < 0.01$) were observed (Table 3). Among the current smokers, heavy smokers who smoked > 2 packs per day had a much higher risk of UC (OR = 4.4, 95% CI = 2.5 to 7.7) compared to never smokers. Among former cigarette smokers, no significant dose-response relationships between the risk of UC and number of cigarettes smoked per day, duration of smoking, or pack-years were observed (data not shown). We observed a statistically significant

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trend between years of quitting and a decreased risk of UC among former smokers, 1-5 years quitting (OR = 2.3, 95% CI = 1.5, 3.5), 5-10 years quitting (OR = 1.2, 95% CI = 0.7, 1.9), 10-20 years quitting (OR = 1.8, 95% CI = 1.2, 2.7), ≥ 20 years quitting (OR = 1.3, 95% CI = 0.8, 2.0, $P_{trend} = 0.04$, where never smokers were the reference).

Waterpipe smoking and bladder cancer risk:

Among men, the prevalence of waterpipe smoking was 25% in UC cases, 27% in SCC cases, and 21% in controls. Those who ever smoked a waterpipe, but did not smoke cigarettes, had a borderline significant association with an increased risk of UC, with an OR of 1.3 (95% CI 1.0 to 1.8); we did not observe such an association in SCC (OR = 1.2, 95% CI = 0.8 to 1.7, Table 2). Among those who smoked waterpipe only, no significant dose-response relationships between the risk of UC and number of hagars smoked per day, duration of smoking, or hagar-years were observed (Table 4). It is important to note that among the men who smoked both waterpipe and cigarettes, the risk of bladder cancer was significantly higher, for both UC and SCC compared to never smokers; OR of 2.9 (2.1 to 3.9) and 1.8 (1.2 to 2.6) were observed, respectively (Table 2).

We were not able to assess the association between active smoking and bladder cancer risk in women because there were only seven women (four cases and three controls) who reported ever smoking cigarettes or waterpipe.

Environmental tobacco smoke (ETS) exposure and bladder cancer risk:

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Overall, the prevalence of ETS exposure was 74% in men and 62% in women. Among male non-tobacco users (defined as men who never smoked a waterpipe or more than 100 cigarettes in their lifetime) ETS exposure, both at home and outside the home, was significantly associated with UC (OR = 2.5, 95% CI = 1.2 to 5.1), but not with SCC (OR = 0.9, 95% CI = 0.3 to 2.5). Among women, ETS exposure both at home and outside the home was non-significantly associated with UC (OR = 1.8, 95% CI = 0.8 to 3.8), and borderline significantly associated with SCC (OR = 2.1, 95% CI = 1.0 to 4.4, Table 5).

Schistosomiasis and bladder cancer risk:

The self-reported history of schistosomiasis revealed different patterns in men and women. Among men, the prevalence of ever being diagnosed with schistosomiasis was 55%, 56%, and 49% for UC cases, SCC cases, and controls, respectively (Table 2). History of schistosomiasis among men was associated with UC (OR = 1.4, 95% CI = 1.2, 1.7) and SCC (OR = 1.4, 95% CI = 1.1, 1.7). Among women, the prevalence of ever being diagnosed with schistosomiasis was lower than for men, 23%, 25%, and 13% for UC cases, SCC cases and controls, respectively. History of schistosomiasis in women was significantly associated with increased risk of both UC (OR = 1.9, 95% CI = 1.2, 2.9) and SCC (OR = 1.9, 95% CI = 1.2, 3.0) (Table 2).

Interactions between schistosomiasis, tobacco smoking, and bladder cancer risk in men:

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Among men, we did not find significant interactive effects on bladder cancer risk between cigarette smoking and history of schistosomiasis ($P = 0.85$), nor between waterpipe smoking and history of schistosomiasis ($P = 0.60$).

DISCUSSION

In this large, multi-center study in Egypt, we found that cigarette smoking moderately increased the risk of bladder UC: male ever-smokers had a 1.8-fold higher risk of UC than males who never smoked. Worldwide, UC is the predominant type of urinary bladder cancer (>90%) and cigarette smoking is a well established risk factor. Overall, ever-smokers have a two- to four-times higher risk of bladder cancer than never smokers in the developed countries (23;24), and the risk tends to increase with increase in smoking duration and intensity (25;26). It should be noted that cigarette smoking habits are different in Egypt compared to the developed countries, and are characterized by lower levels of pack-years and a large proportion of non-daily smokers (20). In our study population, 83% of smokers smoked less than 20 cigarettes (one pack) per day and less than 5% of the smokers smoked 40 cigarettes (2 packs) or more per day, consistent with previous reports of low levels of pack-years smoking among Egyptian men (20). Therefore, the observed association between cigarette smoking and the risk of UC among Egyptian men may partly reflect the overall low levels of exposure. Among current smokers, we also observed that heavy smokers (2 packs or more per day) had 4.4 times higher risk of UC compared to never smokers, indicating that the risk associated with heavy cigarette smoking exposure is comparable to what has been observed in the developed countries (25;26).

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In Egypt, large epidemiological studies to characterize the relationship between cigarette smoking and bladder cancer risk are historically lacking. In a small case-control study (151 male cases and 157 controls) conducted in a single clinical center in Alexandria, Egypt, it was reported that ever smokers had a 4.4-fold of increased risk of bladder cancer (which included all histological types) (21). That earlier study recruited the non-cancer control subjects from patients who were admitted to the same hospital, but excluded those with smoking-related conditions. Such a study design likely resulted in selection bias, which probably inflated the estimated odds ratio. Our study is the first epidemiological study in Egypt with population-based controls and detailed analysis examining the association between cigarette smoking and bladder cancer risk. We found that cigarette smoking is moderately associated with the risk of UC and is not significantly associated with risk of SCC among Egyptian men.

Another unique feature of tobacco smoking in Egypt is the relatively high prevalence (20%) of waterpipe smoking in men, and many Egyptian men smoke both cigarettes and waterpipe (17). Our study provided a unique opportunity to examine the effects of cigarette and waterpipe smoking on bladder cancer risk. In our control population, we found 13% of the men only smoked a waterpipe, 57% only smoked cigarettes, and 8% smoked both cigarettes and waterpipe. We observed no statistically significant association between waterpipe smoking only and bladder cancer risk. This may partly explained by the possibility that such individuals are not strongly addicted to tobacco products, and may be more likely than cigarette smokers to consume modest amounts of tobacco. Importantly, we found that waterpipe smoking and cigarette smoking synergistically increased the odds of having UC (OR = 2.9) or SCC (OR = 1.8) among men, although the mean pack-years was slightly lower in men who smoked both

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cigarettes and waterpipe (mean = 25.9, 34.4, 27.5 for controls, UC and SCC, respectively) than in men who smoked cigarettes only (mean = 33.6, 35.6, 30.5 for controls, UC and SCC, respectively). These findings have potentially important public health implications for Egypt, where the prevalence of waterpipe smoking is about 20% in men (17) and where there is a general perception that waterpipe smoking is less harmful than cigarette smoking (18). This finding is consistent with a previous report of waterpipe smokers having significantly higher level of micronuclei in their exfoliated oral cells compared to non-smokers (27), suggesting a genotoxic effect of waterpipe smoking. To the best of our knowledge, ours is the first study to report that waterpipe smoking modulates the effect of cigarette smoking to significantly increase the risk of both UC and SCC.

We also examined whether exposure to ETS contributes to the risk of bladder cancer, and found that exposures to ETS both at home and outside the home were significantly associated with a 2.5-fold increased risk of UC, but not SCC, among men who never used any tobacco products. ETS exposure both at home and outside the home in women was borderline significantly associated with UC and SCC (Table 5). ETS has been established as a lung carcinogen (28), and a previous study suggested ETS was associated with bladder cancer risk in lifelong nonusers of any tobacco products (29;30), while other studies showed a lack of association between ETS and increased risk of bladder cancer (31;32). In our study population, 62% of women and 74% of men reported exposure to ETS at home or outside the home. ETS exposure is a major public health problem in Egypt because there are several factors that could result in heavy exposure: (i) the majority of the population lives in small homes; (ii) the lack of public health campaigns against smoking in the home and in public places; and (iii) many people

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smoke waterpipes. Our data suggested that heavy exposure (exposed both at home and outside the home) to ETS is a significant risk factor for UC in both men and women, and perhaps for SCC in women.

Regarding SH infection, we found that the history of ever being diagnosed with schistosomiasis was significantly associated with the risk of UC and of SCC in both men and women. SH is a well-established risk factor for SCC (22;33-35), and is classified as a Group 1 carcinogen (2). This parasitic disease, characterized by repetitive infections, causes damage to the bladder and kidneys, and cancer is common in the advanced stages (12;33). It is thought that bladder neoplasia occurs as a result of chronic inflammation, leading to metaplasia. Our data are consistent with these previous reports, and they also suggest that this association is stronger in women than in men (Table 2). Possible explanations include: (i) women received less treatment for their SH infections, resulting in more severe chronic disease; (ii) women may recall their diagnosis and treatment more reliably; (iii) women may be more susceptible to SH-induced bladder carcinogenesis. In our study population, women were significantly less likely than men to receive treatment for SH, either on individual basis or in mass treatment campaigns offered to whole villages (data not shown). Untreated SH infection would lead to severe chronic disease with a known outcome of bladder cancer as its long term sequela. To test the reliability of self-reported data, we examined the concordance between self-reported history of SH and the presence of schistosome ova in tumor specimens among cases, and found that the overall concordance is 58.2% (58.3% for women and 58.2% for men). Thus, misclassification of the exposure is not likely be the major factor contributing to the gender differences in the strength of the association between self-reported history of SH and bladder cancer risk. Whether women are

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more susceptible than men to SH-induced bladder carcinogenesis is a question that remains to be determined and warrants further investigation.

The finding that history of SH is significantly associated with the risk of UC is intriguing. Although SH infection is a well documented risk factor for SCC, its relationship to UC is unclear. A recent case report suggested that SH may be associated with non-squamous cell types of bladder cancer (36). Our data, for the first time, provides evidence that SH infection may contribute to the high incidence of UC among non-smoking Egyptian women.

Our study has several methodological strengths: (i) large sample size, including large numbers of both UC and SCC cases, and a larger number of women with SCC than has been previously reported, which allowed the examination of possible differences in risk factors by gender and histological type; (ii) controls were population-based; (iii) our study had very high participation rates for both cases (84%) and controls (97%), thus with minimal selection bias; (iv) it was a multi-center study that recruited cases from several areas of Egypt; and (v) cases were ascertained as primary bladder carcinoma by the same team of pathologists. There are also weaknesses: (i) despite the large sample size, we still lacked enough women with tobacco exposures to generate precise risk estimates, due to the fact that Egyptian women do not report smoking tobacco products; (ii) there is no reliable biomarker to confirm history of schistosomiasis, so the study had to rely on self-reported data; (iii) infections were self reported, and thus misclassification could have attenuated the estimated odds ratios. We assessed the concordance between self-reported history of schistosomiasis and self-reported history of

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treatment: the concordance was 84.9% for controls and 87.1% for cases, suggesting that misclassification was non-differential.

In summary, this report provided new evidence that the history of schistosomiasis is associated with the risk of UC among non-smoking Egyptian women, and confirms that this parasitic infection is a risk factor for SCC in both men and women. Our results included the novel finding that smoking waterpipes and cigarettes acts synergistically in increasing the risk of both UC and SCC in Egyptian men. The data also suggested that cigarette smoking is only moderately associated with UC risk among Egyptian men; heavy exposure to ETS was associated with UC in both women and men, and perhaps with SCC in women. Exposures to SH among both sexes, and smoking among men, appear to account for some but not all of the differences in sex-based disparities in the incidence of UC and SCC. This ongoing case-control study also aims to shed light on possible genetic and environmental interactions underlying these gender differences in bladder cancer risk factors.

ACKNOLEDGMENTS

The authors thank the Ministry of Health and Population of Egypt, and the Cancer Centers in Cairo, Minia, and Assiut for supporting the study. We are also indebted to the many interviewers, translators, drivers, and other support personnel who made the study possible through their dedicated work. The greatest gratitude goes to all the individuals who participated in our study.

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GRANT SUPPORT

This work was supported by grants from the National Cancer Institute of the U.S. National Institutes of Health (R01-CA115618 to C.A.L., R01-CA132996 to Y.L.Z.).

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Table 1: Social and Demographic Characteristics of Study Population, Egypt, 2006-2010

Host factors	Males			Females		
	Controls (N=2089)	UC cases (N=1023)	SCC cases (N=512)	Controls (N=627)	UC cases (N=174)	SCC cases (N=177)
Age, mean (SD)	57.5 (12.1)	61.3 (10.8)[1]	57.3 (10.6)	54.6 (13.1)	60.2 (11.3)[1]	53.3 (10.8)
Age group, N (%)						
<45	256 (12)	63 (6)	47 (9)	128 (20)	14 (8)	34 (19)
45-55	540 (26)	211 (21)	148 (29)	160 (26)	31 (18)	62 (35)
55-65	637 (31)	327 (32)	185 (36)	185 (29)	61 (35)	51 (29)
>65	656 (31)	422 (41)[1]	132 (26)[1]	154 (25)	68 (39)[1]	30 (17)[2]
Education, N (%)						
None	1062 (51)	685 (67)	410 (80)	465 (74)	153 (88)	162 (92)
Literacy classes/primary school	566 (27)	244 (24)	81 (16)	94 (15)	17 (10)	13 (7)
Preparatory/high/technical school	382 (18)	81 (8)	21 (4)	60 (10)	3 (2)	1 (<1)
College/University	78 (4)	12 (1)[1]	0 (0)[1]	8 (1)	1 (<1)[1]	1(<1)[1]
Marital status, N (%)						
Never Married	38 (2)	8 (<1)	10 (2)	12 (2)	1 (<1)	4 (2)
Married	1944 (93)	965 (94)	479 (94)	400 (64)	94 (54)	109 (62)
Widowed	99 (5)	45 (4)	21 (4)	208 (33)	75 (43)	54 (30)
Divorced	8 (<1)	5 (<1)	2 (<1)	7 (1)	4 (2)[2]	10 (6)
Region of residence, N (%)						
Urban	184 (9)	195 (19)	44 (9)	85 (14)	32 (18)	17 (10)
Rural	1905 (91)	828 (81)[1]	468 (91)	542 (86)	142 (82)	160 (90)

Abbreviations: SCC, Squamous cell carcinoma; UC, Urothelial cell carcinoma

[1] *P value* <0.01 for the comparison with controls (based on χ^2 for frequencies, and *t test* for means)

[2] *P value* <0.05 for the comparison with controls (based on χ^2 for frequencies, and *t test* for means)

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Table 2. Association of Selected Risk Factors with Urothelial (UC) and Squamous Cell Carcinoma (SCC) of the Bladder

Risk Factors	Controls	UC cases			SCC cases		
	N	N	OR[1] (95% CI)	OR[2] (95% CI)	N	OR[1] (95% CI)	OR[2] (95% CI)
MEN ONLY							
*History of schistosomiasis**							
No	1027	449	1.0	1.0	218	1.0	1.0
Yes	1015	564	1.5 (1.3, 1.7)	1.4 (1.2, 1.7)	289	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)
Tobacco use							
Never users	463	127	1.0	1.0	88	1.0	1.0
Waterpipe only	275	108	1.4 (1.0, 1.9)	1.3 (1.0, 1.8)	73	1.4 (1.0, 2.0)	1.2 (0.8, 1.7)
Cigarette only	1189	638	1.9 (1.5, 2.4)	1.8 (1.4, 2.2)	288	1.3 (1.0, 1.7)	1.1 (0.9, 1.5)
Both users	162	150	3.2 (2.3, 4.3)	2.9 (2.1, 3.9)	63	2.0 (1.4, 3.0)	1.8 (1.2, 2.6)
WOMEN ONLY[#]							
*History of schistosomiasis**							
No	535	131	1.0	1.0	129	1.0	1.0
Yes	80	40	2.1 (1.3, 3.2)	1.9 (1.2, 2.9)	44	2.2 (1.5, 3.4)	1.9 (1.2, 3.0)

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Intervals; UTI, Urinary Tract Infection

[1] adjusted for age (in 5-year categories) and governorate of residence

[2] adjusted Odds Ratio (aOR): adjusted for age (5-year categories), governorate of residence, urban/rural residence, education, smoking (men only), history of schistosomiasis, history of UTI other than schistosomiasis, and menopause (women only)

***** History of schistosomiasis missing for 62 male participants (47 controls, 10 UC cases, and 5 SCC cases) and 19 female participants (12 controls, 3 UC cases, and 4 SCC cases)

<5% of women were tobacco users so tobacco use could not be assessed in women

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Table 3. Association of Cigarette Smoking with Urothelial (UC) and Squamous Cell Carcinoma (SCC) of the Bladder Among Egyptian Men[#]

Cigarette Smoking Factors	**Controls* (N=1651)**	**UC cases* (N=765)**			**SCC cases* (N=376)**		
	N	**N**	**OR[1] (95% CI)**	**aOR[2] (95% CI)**	**N**	**OR[1] (95% CI)**	**OR[2] (95% CI)**
Smoking status							
Never	463	127	1.0	1.0	88	1.0	1.0
Former	280	114	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	48	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)
Current	908	524	2.1 (1.7, 2.6)	2.0 (1.6, 2.5)	240	1.4 (1.0, 1.8)	1.2 (0.9, 1.5)
Smoking duration							
Never smokers	463	127	1.0	1.0	88	1.0	1.0
<28 years	265	81	1.3 (0.9, 1.8)	1.4 (1.0, 1.9)	54	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)
28-37 years	301	128	1.7 (1.3, 2.4)	1.7 (1.2, 2.3)	82	1.4 (1.0, 1.9)	1.1 (0.8, 1.7)
38-47 years	340	204	2.0 (1.6, 2.7)	1.9 (1.4, 2.5)	88	1.3 (0.9, 1.8)	1.1 (0.8, 1.6)
>47 years	281	223	2.2 (1.6, 2.9)	2.0 (1.4, 2.6)	64	1.2 (0.8, 1.8)	1.0 (0.7, 1.5)
P trend				*<0.01*			*0.74*
Cigarettes per day							
Never smokers	463	127	1.0	1.0	88	1.0	1.0
1-10	375	220	2.0 (1.6, 2.8)	1.9 (1.5, 2.5)	119	1.6 (1.2, 2.2)	1.4 (1.0, 2.0)
11-20	617	325	1.9 (1.5, 2.6)	1.7 (1.3, 2.2)	138	1.1 (0.9, 1.5)	1.0 (0.7, 1.3)
21-40	139	56	1.3 (0.9, 2.2)	1.3 (0.9, 2.0)	23	0.9 (0.5, 1.4)	0.8 (0.5, 1.4)
>40	54	36	2.3 (1.4, 3.6)	2.2 (1.3, 3.7)	8	0.7 (0.3, 1.6)	0.7 (0.3, 1.5)
P trend				*<0.01*			*0.23*
Pack-years							
Never smokers	463	127	1.0	1.0	88	1.0	1.0
<11	272	119	1.8 (1.4, 2.5)	1.8 (1.3, 2.5)	95	1.8 (1.3, 2.5)	1.6 (1.1, 2.3)
11-23.25	292	156	1.8 (1.4, 2.5)	1.7 (1.3, 2.3)	60	1.1 (0.8, 1.6)	0.9 (0.6, 1.4)
23.25-36.75	329	171	1.9 (1.5, 2.6)	1.8 (1.3, 2.4)	72	1.1 (0.8, 1.5)	0.9 (0.6, 1.3)
>36.75	290	189	1.9 (1.4, 2.5)	1.8 (1.3, 2.4)	61	1.1 (0.7, 1.6)	0.9 (0.6, 1.4)
P trend				*<0.01*			*0.19*

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Intervals

[1] adjusted for age (in 5-year categories) and governorate of residence

[2] adjusted Odds Ratio (aOR): adjusted for age (in 5-year categories), governorate of residence, urban/rural residence, education, history of schistosomiasis, and history of urinary tract infections other than schistosomiasis

<5% of women were tobacco users so tobacco use could not be assessed in women

* Excludes men who reported smoking waterpipes

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Table 4. Association of Waterpipe Smoking with Urothelial (UC) and Squamous Cell Carcinoma (SCC) of the Bladder Among Egyptian Men[#]

Waterpipe Smoking Factors	**Controls* (N=738)**	**UC cases* (N=235)**			**SCC cases* (N=161)**		
	N	**N**	**OR[1] (95% CI)**	**aOR[2] (95% CI)**	**N**	**OR[1] (95% CI)**	**aOR[2] (95% CI)**
status							
Never	463	127	1.0	1.0	88	1.0	1.0
Former	57	25	1.3 (0.7, 2.2)	1.1 (0.6, 1.9)	20	1.8 (1.0, 3.3)	1.7 (0.9, 3.1)
Current	218	83	1.5 (1.1, 2.0)	1.3 (1.0, 1.9)	53	1.2 (0.9, 1.8)	1.0 (0.7, 1.5)
Duration							
Never smokers	463	127	1.0	1.0	88	1.0	1.0
<13 years	37	6	0.7 (0.3, 1.7)	0.6 (0.2, 1.6)	5	0.7 (0.3, 1.9)	0.7 (0.3, 2.0)
13-26 years	65	23	1.8 (1.0, 3.1)	1.6 (0.9, 2.9)	15	1.2 (0.7, 2.3)	0.9 (0.4, 1.7)
27-39 years	92	36	1.6 (1.0, 2.5)	1.4 (0.9, 2.2)	31	1.6 (1.0, 2.6)	1.3 (0.8, 2.2)
>39 years	81	43	1.3 (0.9, 2.1)	1.3 (0.8, 2.0)	22	1.5 (0.9, 2.6)	1.3 (0.7, 2.3)
P trend				*0.11*			*0.31*
Hagars per day							
Never smokers	463	127	1.0	1.0	88	1.0	1.0
1 or less	48	24	1.8 (1.0, 3.1)	1.6 (0.9, 2.9)	11	1.2 (0.6, 3.8)	0.8 (0.4, 1.8)
2-5	147	62	1.5 (1.1, 2.2)	1.4 (1.0, 2.1)	52	1.9 (1.3, 2.8)	1.6 (1.1, 2.5)
6-9	44	16	1.3 (0.7, 2.5)	1.1 (0.6, 2.1)	4	0.5 (0.2, 1.3)	0.3 (0.1, 1.0)
≥10	32	5	0.5 (0.2, 1.5)	0.5 (0.2, 1.3)	5	0.8 (0.3, 2.0)	0.6 (0.2, 1.6)
P trend				*0.79*			*0.88*
Hagar-years							
Never smokers	463	127	1.0	1.0	88	1.0	1.0
<30	41	14	1.7 (0.9, 3.3)	1.3 (0.7, 2.7)	8	1.0 (0.5, 2.3)	0.7 (0.3, 1.7)
30-66	71	36	2.0 (1.2, 3.2)	2.1 (1.3, 3.4)	19	1.3 (0.8, 2.3)	1.2 (0.7, 2.2)
67-153	85	27	1.0 (0.6, 1.7)	0.9 (0.5, 1.5)	35	2.2 (1.4, 3.5)	1.9 (1.1, 3.1)
>153	74	30	1.3 (0.8, 2.2)	1.1 (0.7, 1.9)	10	0.7 (0.3, 1.4)	0.5 (0.2, 1.0)
P trend				*0.48*			*0.79*

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Intervals

[1] adjusted for age (in 5-year categories) and governorate of residence

[2] adjusted Odds Ratio (aOR): adjusted for age (in 5-year categories), governorate of residence, urban/rural residence, education, history of schistosomiasis, and history of urinary tract infections other than schistosomiasis

<5% of women were tobacco users so tobacco use could not be assessed in women

* Excludes participants who reported smoking cigarettes

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Table 5. Association of Environmental Tobacco Smoke (ETS) with Urothelial (UC) and Squamous Cell Carcinoma (SCC) of the Bladder

ETS exposure	Controls	UC cases			SCC cases		
	N	N	OR[1] (95% CI)	aOR[2] (95% CI)	N	OR[1] (95% CI)	aOR[2] (95% CI)
MEN ONLY							
Non-cigarettes smokers#							
None	235	68	1.0	1.0	38	1.0	1.0
Home only	53	32	2.0 (1.2, 3.5)	1.9 (1.1, 3.3)	21	2.7 (1.5, 5.1)	2.4 (1.2, 4.6)
Outside only	352	96	1.1 (0.8, 1.6)	1.1 (0.8, 1.7)	81	1.4 (0.9, 2.2)	1.4 (0.9, 2.2)
Both	98	38	1.7 (1.0, 2.7)	1.6 (1.0, 2.7)	19	1.3 (0.7, 2.4)	1.2 (0.7, 2.4)
*Non-tobacco users**							
None	143	28	1.0	1.0	21	1.0	1.0
Home only	34	14	1.8 (0.8, 4.1)	1.8 (0.8, 4.3)	7	1.4 (0.5, 3.7)	1.5 (0.5, 4.3)
Outside only	232	59	1.4 (0.9, 2.4)	1.4 (0.8, 2.4)	51	1.6 (0.9, 2.8)	1.4 (0.8, 2.6)
Both	54	25	3.0 (1.5, 5.9)	2.5 (1.2, 5.1)	7	1.0 (0.4, 2.5)	0.9 (0.3, 2.5)
WOMEN ONLY							
*Non-tobacco users**							
None	237	71	1.0	1.0	51	1.0	1.0
Home only	315	75	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	94	1.3 (0.9, 1.9)	1.2 (0.8, 1.9)
Outside only	31	8	0.9 (0.4, 2.1)	0.8 (0.3, 2.1)	8	1.1 (0.5, 2.7)	1.0 (0.4, 2.7)
Both	33	15	2.0 (1.0, 4.0)	1.8 (0.8, 3.8)	15	2.0 (1.0, 4.0)	2.1 (1.0, 4.4)

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Intervals

[1] adjusted for age (in 5-year categories) and governorate of residence

[2] adjusted Odds Ratio (aOR): adjusted for age (in 5-year categories), governorate of residence, urban/rural residence, education, cigarette smoking, waterpipe use, history of schistosomiasis, history of UTI other than schistosomiasis, and menopause (women only)

Excludes participants who reported smoking cigarettes

* Excludes participants who reported smoking cigarettes or waterpipe

Author Manuscript Published OnlineFirst on December 6, 2011; DOI: 10.1158/1055-9965.EPI-11-0589
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

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Yun-Ling Zheng, Sania Amr, Doaa Saleh, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst December 6, 2011.

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