Research Article

Urinary Bladder Cancer Risk Factors in Egypt: A Multicenter Case–Control Study

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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 ORs and 95% confidence interval (CI) of the associations.

Results: Among men, cigarette smoking was associated with an increased risk of urothelial carcinoma (OR = 1.8; 95% CI, 1.4–2.2) but not squamous cell carcinoma (SCC); smoking both water pipes and cigarettes was associated with an even greater risk for urothelial carcinoma (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 nonsmoking men and women, environmental tobacco smoke exposure was associated with an increased risk of urothelial carcinoma. History of schistosomiasis was associated with increased risk of both urothelial carcinoma (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 urothelial carcinoma and SCC, respectively) in men.

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

Impact: This study provides new evidence for associations between bladder cancer subtypes and schistosomiasis and suggests that smoking both cigarettes and water pipes increases the risk for SCC and urothelial carcinoma in Egyptian men. Cancer Epidemiol Biomarkers Prev; 21(3); 537–46. ©2011 AACR.

Introduction

The two predominant histologic types of urinary bladder cancer are urothelial and squamous cell carcinoma (SCC). Cigarette smoking, occupational exposures to carcinogens, and chronic infection with Schistosoma haematobium have been established as risk factors for bladder cancer (1–6). In industrialized countries, urothelial cancer (OR = 1.1–1.7, for urothelial carcinoma and SCC, respectively) in men. Among nonsmoking men and women, environmental tobacco smoke exposure was associated with an increased risk of urothelial carcinoma. History of schistosomiasis was associated with increased risk of both urothelial carcinoma (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 urothelial carcinoma and SCC, respectively) in men.

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In the past in Egypt, where S. haematobium was endemic, bladder cancer diagnoses were made at younger ages (<50 years) than in developed countries, and 68% of the cases were identified histologically as SCC (10–12). With the government’s efforts to eradicate S. haematobium and treat infected individuals over the past 3 decades, a shift from SCC to urothelial carcinoma 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 with other regions, is the high prevalence of water pipe smoking.
Furthermore, environmental tobacco smoke (ETS), although established as lung carcinogen (IARC), has not been established as a risk factor for bladder cancer.

To date, epidemiologic investigations of bladder cancer in Egypt have been small studies focused on men (21; 22) from a specific geographic 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 multicenter case–control study to investigate different risk factors potentially associated with this malignancy. In this report, we examine the associations between cigarette and water pipe smoking, ETS exposure, \textit{S. haematobium} infection, and bladder cancer risk, in men and women, separately.

Materials and Methods

The Institutional Review Boards of the 3 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 (Baltimore, MD), Georgetown University (Washington, DC), 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 3 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 and 80 years, 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 (i) I. Gouda and I. Loay who worked together to standardize case classification, and report it as: (i) urothelial carcinoma, (ii) SCC, (iii) adenocarcinoma, or (iv) other, including undifferentiated carcinomas. Carcinoma that metastasized to the bladder was excluded. This report includes only urothelial carcinoma 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.

(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 health care, 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: (i) no known diagnosis of any cancer; (ii) between ages 19 and 80; and (iii) self-identified as able to participate in an interview. Using a portable ultrasound machine, the physician accompanying the recruitment team conducted an abdominal ultrasound examination to rule out any asymptomatic abdominal mass. The interview and phlebotomy were conducted at the participants’ home.

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

Variable definition and statistical analysis

The primary exposures of interest were tobacco use, \textit{S. haematobium} 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,” “water pipe only,” “cigarette only,” and “both water pipe and cigarette.” Participants who had smoked less than...
100 cigarettes in their lifetime and had never smoked a water pipe were classified as “never users”; those who smoked less than 100 cigarettes in their lifetime but reported smoking water pipes were classified as “water pipe only” users; “cigarette only” users were those who had never smoked water pipes but had smoked at least 100 cigarettes in their lifetime; and “both water pipe and cigarette” users were those who reported smoking at least 100 cigarettes in their lifetime and also used water pipes. 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 1 year prior to diagnosis), and “current” smokers; (ii) cigarette smoking duration; (iii) cigarettes smoked per day; and (iv) pack-years of cigarette smoked. Smoking duration, number of cigarette smoked per day, and pack-years of cigarette smoked were divided into quartiles on the basis of distribution among controls, with the referent group being “never users.” Risk of bladder cancer with water pipe use was explored by creating variables similar to those created for cigarette smoking. The tobacco load that is placed on the holder of the water pipe is called a “hagar.” We used 2 variables to represent the dose of water pipe 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-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 water pipe 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 χ² 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 urothelial carcinoma and SCC histologic 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), and history of schistosomiasis or tobacco use (when appropriate). The covariates were selected a priori on the basis of their known association with bladder cancer in this population. Two-way interactions of schistosomiasis with cigarette smoking and water pipe 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 conducted using SAS software, version 9.2 (SAS Institute Inc.).

Results

Characteristics of the study population

From July 2006 through July 2010, a total of 4,049 patients presumed with bladder cancer were approached at the 3 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 nonmalignancies 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 urothelial carcinoma (60%), and 102 other type of primary bladder cancer cases (5%). For this report, we focused on SCC and urothelial carcinoma. 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 controls who reported completing secondary school or higher education. Among men, 95% of cases and 93% of controls were married, whereas 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 primary bladder cancer cases (P < 0.01).

Cigarette smoking and bladder cancer risk

Among men, the prevalence of cigarettes smoking was 77% for urothelial carcinoma cases, 69% for SCC cases, and 65% for controls, as shown in Table 2. Those who reported ever smoking cigarettes, but not water pipes, had a significant association with increased risk of urothelial carcinoma, with an adjusted OR of 1.8 (95% confidence interval CI, 1.4-2.2]. This behavior was not significantly associated with an increased risk of SCC. Importantly,
smokers who smoked both cigarettes and water pipe had a significantly elevated risk of both urothelial carcinoma and SCC, with an OR of 2.9 (2.1–3.9) and 1.8 (1.2–2.6) for urothelial carcinoma and SCC, respectively (Table 2). Among the cigarette smokers, current smokers had significantly elevated risk of urothelial carcinoma, with an OR of 2.9 (2.1–3.9) and 1.8 (1.2–2.6) were observed, respectively (Table 2).

Significant dose–response relationships between the number of cigarettes smoked per day and risk of urothelial carcinoma ($P_{\text{trend}} < 0.01$), between years smoked and risk of urothelial carcinoma ($P_{\text{trend}} < 0.01$), and between pack-years and risk of urothelial carcinoma ($P_{\text{trend}} < 0.01$) were observed (Table 3). Among the current smokers, heavy smokers who smoked >2 packs per day had a much higher risk of urothelial carcinoma (OR = 4.4; 95% CI, 2.5–7.7) than never smokers. Among former cigarette smokers, no significant dose–response relationships between the risk of urothelial carcinoma and number of cigarettes smoked per day, duration of smoking, or pack-years were observed (data not shown). We observed a statistically significant trend between years of quitting and a decreased risk of urothelial carcinoma 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; $P_{\text{trend}} = 0.04$, where never smokers were the reference).

**Water pipe smoking and bladder cancer risk**

Among men, the prevalence of water pipe smoking was 25% in urothelial carcinoma cases, 27% in SCC cases, and 21% in controls. Those who ever smoked a water pipe, but did not smoke cigarettes, had a borderline significant association with an increased risk of urothelial carcinoma, with an OR of 1.3 (95% CI, 1.0–1.8); we did not observe such an association in SCC (OR = 1.2: 95% CI, 0.8–1.7; Table 2). Among those who smoked water pipe only, no significant dose–response relationships between the risk of urothelial carcinoma 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 water pipe and cigarettes, the risk of bladder cancer was significantly higher for both urothelial carcinoma and SCC than in never smokers; ORs of 2.9 (2.1–3.9) and 1.8 (1.2–2.6) 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 7 women (4 cases and 3 controls) who reported ever smoking cigarettes or water pipe.
ETS exposure and bladder cancer risk

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 water pipe or more than 100 cigarettes in their lifetime) ETS exposure, both at home and outside the home, was significantly associated with urothelial carcinoma (OR = 2.5; 95% CI, 1.2–5.1) but not with SCC (OR = 0.9; 95% CI, 0.3–2.5). Among women, ETS exposure both at home and outside the home was nonsignificantly associated with urothelial carcinoma (OR = 1.8; 95% CI, 0.8–3.8) and borderline significantly associated with SCC (OR = 2.1; 95% CI, 1.0–4.4; 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 urothelial carcinoma cases, SCC cases, and controls, respectively (Table 2). History of schistosomiasis among men was associated with urothelial carcinoma (OR = 2.5; 95% CI, 1.2–5.1) but not with SCC (OR = 0.9; 95% CI, 0.3–2.5). Among women, the prevalence of ever being diagnosed with schistosomiasis was lower than for men, 23%, 25%, and 13% for urothelial carcinoma cases, SCC cases, and controls, respectively. History of schistosomiasis in women was significantly associated with increased risk of both urothelial carcinoma (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

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 water pipe smoking and history of schistosomiasis (P = 0.60).

Discussion

In this large, multicenter study in Egypt, we found that cigarette smoking moderately increased the risk of bladder urothelial carcinoma: male ever-smokers had a 1.8-fold higher risk of urothelial carcinoma than males who never smoked. Worldwide, urothelial carcinoma is the predominant type of urinary bladder cancer (>90%) and cigarette smoking is a well-established risk factor. Overall, ever-smokers have a 2 to 4 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 with the developed countries and are characterized by lower levels of pack-years and a large proportion of nondaily smokers (20). In our study population, 83% of smokers smoked less than 20 cigarettes (1 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.
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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 in the first epidemiologic 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 urothelial carcinoma and is not significantly associated with risk of SCC among Egyptian men.

In Egypt, large epidemiologic 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 increased risk of bladder cancer (which included all histologic types; ref. 21). The 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 ORs. Our study is another unique feature of tobacco smoking in Egypt is that among Egyptian men may partly reflect the overall low levels of exposure. Among current smokers, we also observed that heavy smokers (>2 packs per day) had 4.4 times higher risk of urothelial carcinoma than never smokers, indicating that the risk associated with heavy cigarette smoking exposure is comparable with what has been observed in the developed countries (25, 26).

Therefore, the observed association between cigarette smoking and the risk of urothelial carcinoma among Egyptian men and many Egyptian men smoke both cigarettes and water pipe (17). Our study provided a unique

Table 3. Association of cigarette smoking with urothelial and SCC of the bladder among Egyptian men

<table>
<thead>
<tr>
<th>Cigarette smoking factors</th>
<th>Controls $^b$ (N = 1,651)</th>
<th>UC cases $^b$ (N = 765)</th>
<th>SCC cases $^b$ (N = 376)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>OR $^c$ (95% CI)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>463</td>
<td>127</td>
<td>1.0</td>
</tr>
<tr>
<td>Former</td>
<td>280</td>
<td>114</td>
<td>1.2 (0.9–1.7)</td>
</tr>
<tr>
<td>Current</td>
<td>908</td>
<td>524</td>
<td>2.1 (1.7–2.6)</td>
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<tr>
<td>Smoking duration</td>
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<td></td>
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<tr>
<td>Never smokers</td>
<td>463</td>
<td>127</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;28 y</td>
<td>265</td>
<td>81</td>
<td>1.3 (0.9–1.8)</td>
</tr>
<tr>
<td>28–37 y</td>
<td>301</td>
<td>128</td>
<td>1.7 (1.3–2.4)</td>
</tr>
<tr>
<td>38–47 y</td>
<td>340</td>
<td>204</td>
<td>2.0 (1.6–2.7)</td>
</tr>
<tr>
<td>&gt;47 y</td>
<td>281</td>
<td>223</td>
<td>2.2 (1.6–2.9)</td>
</tr>
<tr>
<td>$P_{\text{trend}}$</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>463</td>
<td>127</td>
<td>1.0</td>
</tr>
<tr>
<td>1–10</td>
<td>375</td>
<td>220</td>
<td>2.0 (1.6–2.8)</td>
</tr>
<tr>
<td>11–20</td>
<td>617</td>
<td>325</td>
<td>1.9 (1.5–2.6)</td>
</tr>
<tr>
<td>21–40</td>
<td>139</td>
<td>56</td>
<td>1.3 (0.9–2.2)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>54</td>
<td>36</td>
<td>2.3 (1.4–3.6)</td>
</tr>
<tr>
<td>$P_{\text{trend}}$</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>463</td>
<td>127</td>
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<tr>
<td>&lt;11</td>
<td>272</td>
<td>119</td>
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<td>11–23.25</td>
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<td>23.25–36.75</td>
<td>329</td>
<td>171</td>
<td>1.9 (1.5–2.6)</td>
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<tr>
<td>&gt;36.75</td>
<td>290</td>
<td>189</td>
<td>1.9 (1.4–2.5)</td>
</tr>
<tr>
<td>$P_{\text{trend}}$</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviation: UC, urothelial cell carcinoma.

$^a$Less than 5% of women were tobacco users, so tobacco use could not be assessed in women.

$^b$Excludes men who reported smoking water pipes.

$^c$Adjusted for age (in 5-year categories) and governorate of residence.

$^d$Adjusted OR (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.
opportunity to examine the effects of cigarette and water pipe smoking on bladder cancer risk. In our control population, we found that 13% of the men only smoked a water pipe, 57% only smoked cigarettes, and 8% smoked both cigarettes and water pipe. We observed no statistically significant association between water pipe smoking only and bladder cancer risk. This may partly be 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 water pipe smoking and cigarette smoking synergistically increased the odds of having urothelial carcinoma (OR = 2.9) or SCC (OR = 1.8) among men, although the mean pack-years was slightly lower in men who smoked both cigarettes and water pipe (mean = 25.9, 34.4, 27.5 for controls, urothelial carcinoma, and SCC, respectively) than in men who smoked cigarettes only (mean = 33.6, 35.6, 30.5 for controls, urothelial carcinoma, and SCC, respectively). These findings have potentially important public health implications for Egypt, where the prevalence of water pipe smoking is about 20% in men (17) and where there is a general perception that water pipe smoking is less harmful than cigarette smoking (18). This finding is consistent with a previous report of water pipe smokers having significantly higher level of micronuclei in their exfoliated oral cells than in nonsmokers (27), suggesting a genotoxic effect of water pipe smoking. To the best of our knowledge, ours is the first study to report that water pipe smoking is less harmful than cigarette smoking among men, although the mean pack-years was slightly lower in men who smoked both cigarettes and water pipe (mean = 25.9, 34.4, 27.5 for controls, urothelial carcinoma, and SCC, respectively).
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 urothelial carcinoma, but not SCC, among men who never used any tobacco products. ETS exposure both at home and outside the home were significantly associated with the risk of urothelial carcinoma and SCC (Table 5). ETS has been established as a lung carcinogen (28), and a previous study suggested that ETS was associated with bladder carcinoma and of SCC in both men and women.

Regarding \textit{S. haematobium} infection, we found that the history of ever being diagnosed with schistosomiasis was significantly associated with the risk of urothelial carcinoma and of SCC in both men and women. \textit{S. haematobium} 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 the following: (i) women received less treatment for their \textit{S. haematobium} infections, resulting in more severe chronic disease; (ii) women may recall their diagnosis and treatment more reliably; and (iii) women may be more susceptible to \textit{S. haematobium}–induced bladder carcinogenesis. In our study population, women were significantly less likely than men to receive treatment for \textit{S. haematobium}, either on individual basis or in mass treatment campaigns offered to whole villages (data not shown). Untreated \textit{S. haematobium} 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 *S. haematobium* 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 to be the major factor contributing to the gender differences in the strength of the association between self-reported history of *S. haematobium* and bladder cancer risk. Whether women are more susceptible than men to *S. haematobium*–induced bladder carcinogenesis is a question that remains to be determined and warrants further investigation.

The finding that history of *S. haematobium* is significantly associated with the risk of urothelial carcinoma is intriguing. Although *S. haematobium* infection is a well-documented risk factor for SCC, its relationship to urothelial carcinoma is unclear. A recent case report suggested that *S. haematobium* may be associated with nonsquamous cell types of bladder cancer (36). Our data, for the first time, provide evidence that *S. haematobium* infection may contribute to the high incidence of urothelial carcinoma among nonsmoking Egyptian women.

Our study has several methodologic strengths: (i) large sample size, including large numbers of both urothelial carcinoma 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 histologic 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 multicenter 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 ORs. We assessed the concordance between self-reported history of schistosomiasis and self-reported history of treatment: the concordance was 84.9% for controls and 87.1% for cases, suggesting that misclassification was nondifferential.

In summary, this report provided new evidence that the history of schistosomiasis is associated with the risk of urothelial carcinoma among nonsmoking 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 water pipes and cigarettes acts synergistically in increasing the risk of both urothelial carcinoma and SCC in Egyptian men. The data also suggested that cigarette smoking is only moderately associated with urothelial carcinoma risk among Egyptian men; heavy exposure to ETS was associated with urothelial carcinoma in both women and men and perhaps with SCC in women. Exposures to *S. haematobium* 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 urothelial carcinoma 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.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interests were disclosed.

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**References**

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