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Estrogen exposure and bladder cancer risk in Egyptian women

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Abstract

Objective—To examine associations between reproductive history and urinary bladder cancer in Egyptian women.

Methods—We used questionnaire data from an ongoing, multicenter case-control study in Egypt. Controls were matched on age and residence area. This analysis focused on female cases with confirmed urothelial (UC) and squamous cell (SCC) carcinoma of the bladder.

Results—We recruited 779 women (540 controls, 239 cases; >98.0% nonsmokers). Younger age at menopause (<45 y) and older age at first pregnancy (>18 y) were factors significantly associated with increased risk of bladder cancer, even after adjusting for schistosomiasis history and other covariates in the multivariable logistic model; adjusted odds ratio and 95% confidence intervals were 1.98 (1.41, 2.77) and 6.26 (3.46, 11.34), respectively. On the other hand, multiple pregnancies or use of oral contraceptives were associated with decreased odds of having bladder cancer. Similar associations were observed with UC and SCC when analyzed separately; however, the magnitude of association with SCC was lower than with UC.

Conclusion—Our data suggest that early estrogen exposure, or the relative lack of it, plays a role in urinary bladder carcinoma development among Egyptian women.

Keywords

estrogen; bladder cancer; Egypt; epidemiology; risk factors

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1. Introduction

Urinary bladder cancer, overall the 9th most common malignancy worldwide, affects more men than women [1–4]. The age-standardized incidence rate is 10.1 for men and 2.5 for women per 100,000 p-y [4, 5]. Urothelial (transitional) cell and squamous cell carcinomas (UC and SCC, respectively) are the two predominant histological types of bladder cancer. UC, which occurs at older ages (> 60 y) than SCC and accounts for more than 90% of bladder malignancies in industrialized countries [6], is associated with cigarette smoking and occupational exposures. SCC constitutes up to 75% of cases in some Middle Eastern and African countries with endemic schistosomiasis, which is recognized as a major contributing factor to chronic bladder inflammation and malignancy [7, 8].

In Egypt, smoking is more widespread among adult males (22% to 47%) than females (2% to 7%) [9–13], and bladder cancer is the most common malignancy among Egyptian men, who bear the highest incidence rate worldwide (37.1 per 100,000 p-y) [1]. However, previous research findings indicate that smoking fails to fully account for the male excess observed with this malignancy [4, 6, 13–15]. Also, despite the country's 1980s schistosomiasis eradication campaign, the same 1:4 female-to-male bladder cancer incidence ratio that existed prior to the campaign has persisted. Thus, greater smoking among the men, as well as a legacy effect of schistosomiasis, only partially explain Egypt's gender-disproportionate bladder cancer incidence.

The quest to identify factors associated with the sex difference in bladder cancer incidence has prompted investigations into the role of estrogen exposures, but the findings of such epidemiological studies have been inconsistent [16–23]. To shed further light on the question of why bladder cancer affects more men than women, we examined associations between reproductive history-related estrogen exposures and urinary bladder cancer in Egyptian women, using questionnaire data from an ongoing multicenter case-control study in Egypt. We had a unique opportunity to compare and contrast UC and SCC regarding these potential risk factors.

2. Subjects and methods

2.1 Source study and population

The source study (“Gender Differences in Bladder Cancer Risk Factors”) used a case-control design, with recruitment sites in three major referral centers for Egypt's bladder cancer patients: the National Cancer Institute in Cairo, The Oncology Center at Minia University, and The South Egypt Cancer Institute in Assiut. Institutional Review Boards of the three recruitment sites, the University of Maryland, Baltimore, and Georgetown University approved the study.

2.2 Eligibility and ascertainment of cases

Patients referred to the departments of urology, radiation therapy, or surgery were approached by trained recruiters and offered participation in the study. Eligibility criteria included bladder cancer diagnosis within 1 y and age of >18 y. The recruiters obtained informed consents and enrolled only those patients who self-identified as capable of completing a 20-min interview. One of the study's two pathologists from the NCI of Cairo University reviewed the pathology materials for each case and classified the tumor as UC, SCC, adenocarcinoma, or other types of carcinoma of the urinary bladder; those with other tumors and metastases were excluded. We included only those with UC and SCC (95% of the cases) in this study.

2.3 Control selection

Non-cancer controls were randomly selected from the general population to frequency-match the cumulative group of cases by sex, 5-year age-group, and governorate of residence. The study recruiters obtained the Ministry of Health's approval, visited each selected village within these governorates, and approached the occupants of houses on each randomly chosen street. The recruitment team moved to the next house if none of the residents matched the required sex and age-groups. In the home, the trained interviewer explained the purpose of the study and consented the individual. On each prospective participant, the study physician who accompanied the recruitment team performed abdominal ultrasound, a procedure not commonly provided at the local health clinics although helpful in revealing abdominal anomalies. The study physician used the ultrasound results to exclude those with questionable tumor-like masses in the bladder, referring each individual with abnormal findings to the nearest governmental health unit for follow-up.

2.4 Data collection

The study questionnaire was translated into Arabic, back-translated into English to minimize language-related discrepancies, field-tested, and adjusted for cultural appropriateness. Questioning the cases and controls face-to-face, the trained interviewers collected data on sociodemographic characteristics; smoking and exposure to environmental tobacco smoke (ETS) at home and elsewhere; and medical history, including history of schistosomiasis, as well as other urinary tract infections (UTIs). Women were queried for reproductive history-related estrogen exposures, including age at first pregnancy, numbers of pregnancies and babies delivered, breastfeeding history, contraceptive use, menopausal status, and age at menopause if menses had stopped. No proxy interviews were conducted.

2.5 Variable definitions and statistical analyses

The variables collected from the questionnaire were used as continuous or categorical in the exploratory analyses.. We used X^2 and t tests to determine the significance of associations in the bivariate analysis.. Unadjusted and adjusted odds ratios (UORs and AORs, respectively), and 95% confidence intervals (CIs) were calculated. Using unconditional logistic regression, we analyzed the associations between each estrogen-related variable (main predictor) and the outcome (bladder cancer case vs. control), separately. The variables exhibiting significant associations with bladder cancer risk in the bivariate analysis were assessed for interaction with the main predictor using the Breslow-Day test and were included in the final models. One model included all cases and controls, and two others included all controls and either SCC or UC cases, respectively.

3. Results

The present study sample consisted of 779 women [239 confirmed cases (SCC: 51.7%; UC: 48.3%) and 540 controls]. More than half of the cases (55.6%) and controls (52.8%) were between 50 and 65 y old, with a mean of 56.8 y for cases and 55.3 y for controls (Table 1). Although the majority of the overall sample (>98.0%) reported never having smoked cigarettes or shisha (waterpipe) themselves, more cases than controls (10.2% vs. 3.9%) reported ETS exposure. More cases than controls had a history of schistosomiasis (23.0% vs. 11.9%) and other UTI (19.7% vs. 12.4%). The majority of cases and controls lived in Upper Egypt (86.6% and 92.8%, respectively) and had no schooling (91.2% and 79.1%, respectively). Fewer cases (58.6%) than controls (63.2%) were married.

More controls than cases were still menstruating (29.5% vs. 11.3%), whereas more cases than controls (33.2% vs. 20.8%) reported having reached menopause at an age of <45 years (Table 2). Although the age at first pregnancy ranged from 12 y to 40 y among both groups,

the mean among cases (19.7 y) significantly exceeded that among controls (18.5 y) ($p < 0.0002$). The number of pregnancies varied up to 25 among controls but only up to 16 among cases. The majority of women (>97.0%) breastfed their babies, and the mean breastfeeding times per infant were 22 and 21 months among controls and cases, respectively.

The bivariate analysis revealed significant associations between menopausal status (UOR: 3.3; 95% CI: 2.1, 5.1), history of schistosomiasis (UOR: 2.3; 95% CI: 1.6, 3.5), and older age (>18 y) at first pregnancy (UOR: 2.0; 95% CI: 1.4, 2.7) and increased bladder cancer risk. Greater number of babies delivered (>6) had a marginally significantly protective effect (UOR: 0.7; 95% CI: 0.5, 1.0), and oral contraceptive use was associated with significantly decreased odds (UOR: 0.5; 95% CI: 0.3, 0.7) of bladder cancer. Given that >60% of all cases and controls reported exposure to ETS either inside or outside the home, or in both places, we assessed the relationships between any versus no ETS exposure and the odds of having bladder cancer. We found UORs and 95% CIs of 1.16 (0.84, 1.61), 1.41 (0.91, 2.20), and 1.21 (0.78, 1.88) for all cancer cases, SCC, and UC respectively.

Among the postmenopausal women, early menopause (at <45 y) was significantly associated with greater odds of bladder cancer (UOR: 1.9; 95% CI: 1.3, 2.8), as was history of schistosomiasis (UOR: 2.2; 95% CI: 1.4, 3.5). Oral contraception (UOR: 0.5; 95% CI: 0.3, 0.7) was protective.

In multivariable logistic regression models, we further examined the effect of each of the estrogen-related variables on bladder cancer risk among all women. The AORs and 95% CI of different predictors after adjusting for age, residence area, history of schistosomiasis, and history of UTI remained statistically significant and in the same respective directions (Table 3). No significant interactions were found. In separate models of SCC cases and UC cases (Table 3), the respective directions of the associations between different estrogen-related variables and odds of having any bladder cancer remained the same, but their magnitudes varied. In general, the associations of early menopause and multiple pregnancies with odds of having cancer were stronger for UC and weaker for SCC.

4. Discussion

We evaluated associations between reproductive history-related estrogen exposure and bladder cancer risk in Egyptian women, and we found that older age at first pregnancy (at >18 y) and early menopause (at <45 y) were associated with increased odds of having bladder cancer, and especially the UC type, among those with early menopause. On the other hand, even after adjustment for schistosomiasis history, one of the known risk factors for SCC, oral contraceptive use was associated with lower risk of both bladder cancer types, and multiple pregnancies with lower risk of UC.

Our finding of increased odds of bladder cancer with early menopause is consistent with previously reported results in other studies [16, 18]. Other investigators reported no significant relationships between age at menopause, age at first birth, or parity, and risk of bladder malignancy [17]. Among women who never smoked, Cantor et al. [21] reported decreased risk with increasing parity and with older age at first pregnancy. In our study sample, >98% of whom never smoked, increasing number of pregnancies (parity) was protective, but older age at first pregnancy was associated with greater odds of having either UC or SCC bladder cancer.

Age at menarche, which is commonly used as a surrogate for estrogen exposure, was reported by McGrath et al. [11] and Prizment et al. [9] as not significantly associated with

bladder cancer risk. In our study, the query of age at menarche was removed after field-piloting the questionnaire because of non-differential reporting inaccuracy.

Previous investigators have addressed the effect of postmenopausal hormone therapy (HT) in assessing estrogen exposure and bladder cancer risk. Non-significant associations between HT use and bladder cancer risk [17, 18], as well as significantly decreased [19] and increased [20] risk, have been reported. HT use was rarely reported by our study participants. In our study, we also found a significant association between birth control use and reduced odds of bladder cancer overall, as well as either SCC or UC. Given the small number of cases who took oral contraceptives, the data should be interpreted with caution.

ETS is an established lung carcinogen [24] and a suspected risk factor for bladder cancer among nonsmokers [25]. Previous investigators did not detect significant associations between adult ETS exposure and increased risk of bladder cancer [26, 27]. We found that ETS, to which more than 60% of the women in our sample reported exposure, was associated with high overall bladder cancer risk, although not statistically significantly (UOR: 1.16; 95% CI: 0.84, 1.61), and the risk was higher for SCC than for UC (UOR: 1.41; 95% CI: 0.91, 2.20; UOR: 1.21; 95% CI: 0.78, 1.88, respectively).

Schistosomiasis is another known risk factor for bladder cancer, particularly for SCC among men [28–30]. Very few studies have addressed the role of schistosomiasis in SCC among women. In women with schistosomiasis history, we observed an increased SCC risk (UOR: 2.3; 95% CI: 1.6, 3.5) that remained comparable in all models addressing the estrogen-related variables.

The present study relied on self-reported reproductive history and, therefore, is subject to potential recall bias. While we had no information with which to evaluate this possibility, we believe that non-differential recall error between cases and controls is more likely, wherein the accuracy of reported age at menopause may differ between women with longer versus shorter time since the menses stopped, regardless of case status. The women in our study were unlikely to be aware of prior research findings on possible associations of bladder cancer with the risk factors we ascertained.

5. Conclusion

In conclusion, we found that in nonsmoking Egyptian women, early menopause (at <45 y), and older age at first pregnancy (at >18 y), both markers of low lifetime estrogen exposure, were significantly associated with increased risk of bladder cancer, particularly the UC type, whereas oral contraceptive use was associated with decreased risk. Such associations may help to explain persistent sex differences in the incidence of bladder cancer.

Abbreviations

AOR	adjusted odds ratio
CI	confidence interval, p-y, person-years
SCC	squamous cell carcinoma
UOR	unadjusted odds ratio
UC	urothelial [cell] carcinoma

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Table 1

Sociodemographic characteristics, medical history, and tobacco smoke exposure among female bladder cancer controls and cases in Egypt

Characteristic	Controls N = 540 n (%)	Cases N = 239 n (%)	p-value
Age category (y)			
<50	154 (28.5)	54 (22.6)	0.20
50 to 65	285 (52.8)	133 (55.6)	
>65	101 (18.7)	52 (21.8)	
Mean age $\pm$ SD (y)	55.3 $\pm$ 12.5	56.8 $\pm$ 11.7	0.10
Area of residence			
Other than upper Egypt	39 (7.2)	32 (13.4)	<0.0001
Upper Egypt	501 (92.8)	207 (86.6)	
Marital status			
Married	341 (63.2)	140 (58.6)	0.002
Widowed	186 (34.4)	83 (34.7)	
Divorced or separated	5 (0.9)	13 (5.4)	
Not married	8 (1.5)	3 (1.3)	
Education			
None	427 (79.1)	218 (91.2)	0.0004
Literacy classes or primary school	77 (14.3)	17 (7.1)	
Preparatory, high, or technical school	32 (5.9)	3 (1.3)	
College or university	4 (0.7)	1 (0.4)	
Environmental tobacco smoke exposure			
None	208 (38.9)	87 (37.2)	0.003
Either inside or outside of the home	306 (57.2)	123 (52.6)	
Both inside and outside of the home	21 (3.9)	24 (10.2)	
(Missing 10)			
Cigarette smoking	539 (99.8)	235 (98.3)	
Never	1 (0.2)	1 (0.4)	0.03
Former	0 (0)	3 (1.3)	
Current			
Shisha/waterpipe smoking			
Never	536 (99.3)	236 (98.7)	0.01
Former	4 (0.7)	0 (0)	
Current	0 (0)	3 (1.3)	
Schistosomiasis history			
No	438 (81.1)	162 (67.8)	0.0001
Yes	64 (11.9)	55 (23.0)	
Unknown	38 (7.0)	22 (9.2)	
Urinary tract infection other than schistosomiasis			
No	473 (87.6)	192 (80.3)	0.008

Characteristic	Controls N = 540	Cases N = 239	p-value
	n (%)	n (%)	
Yes	67 (12.4)	47 (19.7)	

Table 2

Reproductive history-related estrogen exposure among female bladder cancer controls and cases in Egypt

Variable	Controls N = 540 n (%)	Cases N = 239 n (%)	p-value
Menopause			
No	159 (29.5)	27 (11.3)	<0.0001
Yes	380 (70.5)	211 (88.7)	
At age (y)			
50	179 (47.1)	70 (33.2)	0.0007
45 to 49	122 (32.1)	71 (33.6)	
<45	79 (20.8)	70 (33.2)	
(Missing 2)			
Age at first pregnancy (y)			
(mean $\pm$ SD)	18.5 $\pm$ 4.1	19.7 $\pm$ 3.8	0.0002
18	306 (59.7)	96 (41.9)	<0.0001
>18	207 (40.3)	133 (58.1)	
(Missing 37)			
Number of pregnancies			
(mean $\pm$ SD)	7.8 $\pm$ 3.6	7.1 $\pm$ 3.0	0.009
7	282 (52.2)	141 (59.0)	0.08
>7	258 (47.8)	98 (41.0)	
Number of babies delivered			
(mean $\pm$ SD)	6.2 $\pm$ 2.7	5.8 $\pm$ 2.6	0.08
6	302 (58.6)	151 (65.7)	0.07
>6	213 (41.4)	79 (34.3)	
(Missing 34)			
Breastfeeding			
No	14 (2.7)	6 (2.6)	0.9
Yes	501 (97.3)	224 (97.4)	
(Missing 34)			
Oral contraceptive use			
No	354 (66.7)	191 (81.6)	<0.0001
Yes	177 (33.3)	43 (18.4)	
(Missing 14)			
Birth control injection use			
No	439 (82.7)	196 (85.6)	0.32
Yes	92 (17.3)	33 (14.4)	
(Missing 19)			

Table 3
Associations between different estrogen-related variables and the risk of bladder cancer among Egyptian women

Estrogen-related main predictor variable ^a	Controls		All Cases		Only SCC ^b		Only UC ^c	
	N	AOR ^d (95% CI) ^{e,f}	N	AOR (95% CI) ^f	N	AOR (95% CI) ^f	N	AOR (95% CI) ^f
Age at first pregnancy (y)								
18	282	ref	45	ref	42	ref		
>18	198	1.98 (1.41, 2.77)	62	1.98 (1.27, 3.09)	59	1.99 (1.25, 3.18)		
Number of pregnancies								
7	257	ref	67	ref	59	ref		
>7	236	0.66 (0.47, 0.94)	44	0.76 (0.48, 1.20)	43	0.62 (0.39, 0.99)		
Menopause								
No	152	ref	17	ref	4	ref		
Yes								
At age (y)								
50	160	2.71 (1.39, 5.29)	22	2.22 (0.91, 5.44)	38	6.13 (1.86, 20.16)		
45 to 49	109	4.06 (2.20, 7.49)	35	4.28 (1.98, 9.24)	29	7.46 (2.35, 23.67)		
<45	72	6.26 (3.46, 11.34)	37	5.63 (2.74, 11.57)	31	12.78 (4.05, 40.29)		
Oral contraceptive								
No	316	ref	89	ref	82	ref		
Yes	168	0.44 (0.29, 0.65)	19	0.36 (0.21, 0.63)	19	0.58 (0.33, 1.03)		

^aFor each main predictor variable, we performed a logistic regression model;

^bsquamous cell carcinoma;

^curothelial [cell] carcinoma;

^dadjusted odds ratio;

^econfidence interval;

^fadjusted for age, residence, history of schistosomiasis, and history of urinary tract infection.