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Nonoccupational exposure to agricultural work and risk of urinary bladder cancer among Egyptian women

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ABSTRACT

This study examined the associations between nonoccupational exposure to agricultural work, through husband or head of household (H/HH) occupation, and urinary bladder cancer risk among Egyptian women. A total of 1,167 women (388 bladder cases and 779 age- and residence-matched, population-based controls) from a multicenter case-control study were included in the analysis. Adjusted odds ratios (*AOR*s) and 95% confidence intervals (CIs) were estimated using logistic regression. Among married women, those who reported H/HH to be an agricultural worker were at increased risk for bladder cancer as compared to those with H/HH in other occupations, *AOR* = 1.54, 95% CI [1.09, 2.18]; among unmarried women the risk was not increased, *AOR* = 0.77, 95% CI [0.45, 1.32]. Nonoccupational exposure to agricultural work, defined as living with an agricultural worker, increased the risk for bladder cancer among married Egyptian women.

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Agricultural worker; bladder cancer; Egypt; nonoccupational exposure; women

Urinary bladder cancer is the seventh-most common malignancy worldwide.[1] Cigarette smoking, occupational exposure to carcinogens, and *Schistosoma haematobium* (SH) infection are well-established risk factors for the main histological types of this malignancy, urothelial cell carcinoma (UC) and squamous cell carcinoma (SCC).[2–8]

Egypt, where both smoking and history of SH are highly prevalent,[8–10] has some of the highest bladder cancer rates in the world among men.[1] Despite the countrywide educational and treatment campaigns in the 1980s aimed at eradicating SH, and the efforts to promote smoking cessation, overall bladder cancer rates have remained elevated. In 2014, the age-standardized incidence rate (SIR) was 21.1 per 100,000 person years among men, but much lower among women, with a female to male ratio of 1:4,[1] a ratio that existed prior to the educational and treatment campaigns and despite the fact that smoking is highly prevalent among men, but not women, in Egypt. Therefore, more prevalent smoking among the men and a legacy effect of schistosomiasis only partially explain Egypt's gender-disproportionate bladder cancer incidence. In searching for other occupational and environmental factors that are associated with bladder cancer risk and its gender difference, we conducted a multicenter case-control study of "Gender differences in bladder cancer risk factors" in Egypt.[8] In nonsmoking Egyptian women, we found early menopause (at < 45 years), and older age at first pregnancy (at > 18 years), both proxies of low lifetime estrogen exposure, to be significantly associated with increased risk of bladder cancer,[11] findings that were reported by others.[12] We also examined agricultural work and found (1) an increased bladder cancer risk among male workers,[13] (2) pesticide exposure as a contributing factor,[14] and (3) a non–statistically significant elevated risk among women living in a household with agricultural workers.[13] These women are likely to be exposed to residues from chemicals and other materials brought home on the farmers' clothes or shoes[15–17] by virtue of the women's traditional responsibility for cleaning the clothes and house. In addition, farmers and their families live in communities close to where they work; therefore, family members may be further exposed to hazards through polluted air and contaminated food or drink.[18,19]

Farming has been investigated in Europe and the United States through ecological and other observational epidemiological studies.[18–29] Nonoccupational exposures to farming and pesticides, particularly among populations living in agricultural areas, have been investigated in children and women.[30,31] Among the latter group, increased risk for leukemia,[32,33] multiple myeloma,[29] and

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other cancers,[34] but not bladder, were reported. To better investigate the risk of urinary bladder cancer (overall, SCC, and UC) and nonoccupational exposure to agricultural work among Egyptian women, we analyzed the information collected from a multicenter case-control study.[8] In the present analysis, we report the associations between bladder cancer risk and living with a husband or head of household (H/HH) who is an agricultural worker, after adjustment for multiple contributing factors to this malignancy among women, including use of pesticides at home and reproductive history.

Methods

Study population

We used data from a case-control study conducted between 2006 and 2014 that addressed risk factors associated with urinary bladder cancer in Egypt. Study recruitment has been described elsewhere;[8] briefly, adults aged 19 to 80 with presumed bladder cancer were recruited from 3 referral cancer centers. One of the 2 study pathologists ascertained the histopathology (primary urinary bladder cancer) and classified each case as UC, SCC, adenocarcinoma, or undifferentiated carcinoma. Controls with no known diagnosis of cancer were randomly selected either from case neighborhoods or through medical records from primary care health clinics located in each governorate; they were frequency matched to cumulative groups of bladder cancer cases on sex, age within 5 years, and area of residence. The present analysis is restricted to the female participants and cases with UCC, SCC, and adenocarcinoma as these are the bladder cancer types that were previously examined for their risk factors in Egypt.[8,13,14,35]

The parent study was approved by the Institutional Review Boards of University of Maryland, Baltimore; Georgetown University; and the 3 referral centers in Egypt. For this analysis, we used the previously collected and deidentified data set.

Data collection

After obtaining informed consent from the study participants, the same structured questionnaire was administered to both the cases and controls by a trained interviewer. Data were collected on sociodemographic characteristics such as age, residence location, marital status, education, working outside the home and the type of occupation, smoking history, and exposure to environmental tobacco smoke (ETS). History of schistosomiasis and urinary tract infection were also documented. Information on environmental exposure to pesticides at home or at work was obtained. Women were also asked about their reproductive history (age at first childbirth, menopausal status, age at menopause, number of pregnancies and born children), and the occupation of the husband or head of household (H/HH). For cultural reasons, unmarried women in Egypt tend to live with their parents or other members of the family, rather than alone.

Data analysis

The dependent variable in this analysis was primary bladder cancer as discussed. The exposure of interest was the participant's H/HH type of work. Female participants were asked about their H/HH's occupation, which included several categories, such as agricultural worker, manual laborer, mechanic, clerical worker, student, merchant or trade worker, or shepherd. For this analysis, the H/HH occupation was dichotomized as agricultural worker versus other.

Covariates examined for potential confounding included marital status, education, smoking status, pesticide use at home, history of schistosomiasis, age at first pregnancy (which was found to be associated with bladder cancer risk in early studies),[11,12] history of urinary tract infection, and ETS exposure. A bivariate analysis was performed to assess the association between each covariate and case-control status, using Student's t test for continuous variables and the chi-square test for categorical covariates.

Logistic regression that included the matching variables of age and location was used to estimate the associations between the independent variables and case-control status. We used a stepwise approach to build a multivariable model that included significant covariates. Further, interaction terms were added to the model to assess covariates as possible effect modifiers. We also built separate models for SCC and UC, but not for adenocarcinoma cases because the number of the latter was too small ($N = 28$) for a meaningful analysis; however, we included those cases in the "all cases" model. In a recent analysis, Amr et al. reported the risk factors for bladder adenocarcinoma in Egypt to be similar to those of SCC and UC.[35]

Unadjusted odds ratios (*OR*s), adjusted odds ratios (*AOR*s), and 95% confidence intervals (CIs) were reported. Approximately 4% of our sample was missing the exposure of interest (H/HH occupation; $n = 51$). In a sensitivity analysis, we conducted a sequential regression multivariate imputation for missing exposure using 5 replicate data sets.[36] All statistical analyses were performed using SAS version 9.3 (The SAS Institute, Cary, NC).

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Results

A total of 454 women were enrolled as bladder cancer cases and frequency matched to 835 controls on age (± 5 years) and location (urban vs rural and north vs south Egypt). Of the case participants, 15 were excluded due to diagnosis with cancers other than SCC, UC, or adenocarcinoma types of primary bladder. As few women in this sample reported their own occupations as farmers (17 cases and 11 controls) and because we were interested in exploring the association between bladder cancer risk and nonoccupational exposure to agricultural work, these women were excluded.

The study sample comprised 422 cases (204 SCC, 190 UC, and 28 adenocarcinomas) and 824 controls; of these participants, 39 cases and 102 controls worked outside the home. The characteristics of the whole sample are displayed in Table 1. Cases tended to be slightly older than controls, with mean (*SD*) age of 55.8 (11) compared to 54.5 (12). Cases were more likely to (1) report that their H/HH was an agricultural worker, (2) be not married (mainly widows), (3) have less education, and (4) be over 18 years of age at their first pregnancy; they were less likely than controls to have used pesticides at home. For the bivariate and final analyses, we excluded the few

Table 1. Sociodemographic characteristics and medical histories of Egyptian women bladder cancer cases and controls.

Characteristic	Control $N = 824$	All cases* $N = 422$	SCC cases $N = 204$	UC cases $N = 190$
Age (years)				
Mean	54.5	55.8	53.2	59.0
SD	12	11	11	11
	N (%)	N (%)	N (%)	N (%)
H/HH occupation				
Other	552 (67)	252 (60)	118 (58)	115 (60)
Agricultural worker	241 (29)	150 (35)	77 (38)	64 (34)
Missing	31 (4)	20 (5)	9 (4)	11 (6)
Area of residence				
Urban	106 (13)	57 (14)	19 (9)	35 (18)
Rural	718 (87)	365 (86)	185 (91)	155 (82)
Area of residence				
North (lower)	80 (10)	56 (13)	26 (13)	28 (15)
South (upper)	744 (90)	366 (86)	178 (87)	162 (85)
Marital status				
Married	549 (67)	244 (58)	122 (60)	103 (54)
Never married	13 (2)	8 (2)	7 (3)	1 (0)
Divorced/separated	11 (1)	17 (4)	10 (5)	5 (3)
Widow	251 (30)	153 (36)	65 (32)	81 (43)
Education				
None	606 (74)	381 (90)	187 (92)	168 (88)
Kottab or primary school	201 (26)	33 (8)	14 (7)	18 (9)
Prep, high, or tech school	84 (10)	6 (1)	2 (1)	3 (2)
College/university	11 (1)	2 (1)	1 (0)	1 (1)
Missing	2 (0)	0 (0)	0 (0)	0 (0)
Smoking (cigarettes or water pipe)				
Both	0 (0)	1 (0)	0 (0)	0 (0)
Cigarettes only	3 (1)	7 (2)	3 (1)	3 (2)
Water pipe only	11 (1)	6 (1)	4 (2)	2 (1)
Neither	810 (98)	408 (97)	197 (97)	185 (97)
ETS exposure among nonsmokers				
No	166 (20)	95 (23)	43 (22)	45 (24)
Yes	597 (74)	306 (75)	151 (77)	136 (74)
Missing	47 (6)	7 (2)	3 (1)	4 (2)
Pesticide use at home				
No	529 (64)	324 (77)	160 (78)	142 (75)
Yes	292 (35)	96 (24)	44 (22)	48 (25)
Missing	3 (0)	0 (0)	0 (0)	0 (0)
History of schistosomiasis				
No	683 (83)	296 (70)	144 (71)	136 (72)
Yes	98 (12)	91 (22)	41 (20)	39 (20)
Unknown	43 (5)	35 (8)	19 (9)	15 (8)
History of UTI				
No	682 (83)	322 (76)	161 (79)	143 (75)
Yes	142 (17)	100 (24)	43 (21)	47 (25)
Age at first pregnancy (years)				
≤18	438 (53)	176 (42)	86 (42)	76 (40)
>18	346 (42)	225 (53)	109 (53)	110 (54)
Missing	40 (5)	21 (5)	9 (4)	12 (6)

Note. SD = standard deviation; ETS = environmental tobacco smoke; H/HH = husband/head of household; SCC = squamous cell carcinoma; UC = urothelial carcinoma; UTI = urinary tract infection.
*All cases included SCC, UC, and adenocarcinoma.

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women (14 cases and 14 controls) who reported ever smoking either cigarettes or water pipes and those who were missing the exposure (H/HH occupation; 20 cases and 31 controls). Therefore, the final study sample consisted of 388 cases and 779 controls. Education and marital status were dichotomized to some education versus none and married versus not married, respectively, for further analyses due to sparse cell sizes. The women who worked outside the home were similar to those who did not except for the type of their H/HH occupation; the majority of the cases reported agriculture, while the majority of the controls reported clerical types of work.

As shown in Table 2, having an agricultural worker for an H/HH was significantly associated with primary bladder cancer overall and the SCC type, *OR* = 1.39, 95% CI [1.07, 1.81, and *OR* = 1.47, 95% CI [1.05, 2.06], respectively. Although the odds of having UC type of bladder cancer among women whose H/HHs were agricultural workers as compared to other occupations were elevated, the odds ratio was not statistically significant (OR = 1.39, 95% CI [0.97, 1.99]). Of the covariates, marital status, education, pesticide use at home, history of schistosomiasis, and age at first pregnancy were included in the multivariable model. History of UTI was not included because it did not materially alter the *OR*s for H/HH worker effect.

Using a stepwise approach to build the multivariable regression model, we found that the odds of having any bladder cancer among women whose H/HHs were agricultural workers were higher than the odds for those whose H/HHs were not, after adjustment for the matching variables, marital status, education, pesticide use at home, history of schistosomiasis, and age at first pregnancy (*AOR* = 1.26, 95% CI [0.94, 1.68]), albeit these results were not statistically significant. Similarly, the odds of having UC (*AOR* = 1.34, 95% CI [0.91, 1.99]) and SCC (*AOR* = 1.28, 95% CI [0.89, 1.99]) were also elevated after adjustment for the same covariates. In addition, when we added marital status to the model, the main effect significantly changed; we found that the interaction term (marital status * H/HH occupation) was statistically significant (p =.03) when added to the fully adjusted model for all cases (Table 3). The interaction term was not statistically significant for either SCC or UC in the fully adjusted models (p =.13 and .11, respectively). As shown in Table 3, married women who reported their H/HH to be an agricultural worker, compared to those who reported other occupations, had significantly higher odds of having bladder cancer, even after adjustment for several covariates (*AOR* = 1.54, 95% CI [1.09, 2.18] for all cases; *AOR* = 1.53, 95% CI [0.99, 2.38] for SCC; and *AOR* = 1.66, 95% CI [1.03, 2.69] for UC); the odds of having bladder cancer among unmarried women were not increased (*AOR* = 0.77, 95% CI [0.45, 1.32] for all cases; *AOR* = 0.82, 95% CI [0.41, 1.64] for SCC; *AOR* = 0.87, 95% CI [0.44, 1.70] for UC).

Table 2. Odds ratios and 95% confidence intervals of the associations between study variables and bladder cancer among Egyptian women.

	All cases* $N = 388$		SCC cases $N = 188$		UC cases $N = 174$	
Variable	*OR*	95% CI	*OR*	95% CI	*OR*	95% CI
H/HH occupation						
Other		Reference		Reference		Reference
Agricultural worker	1.39	1.07, 1.81	1.47	1.05, 2.06	1.39	0.97, 1.99
Marital status						
Not married		Reference		Reference		Reference
Married	0.66	0.50, 0.87	0.59	0.41, 0.84	0.74	0.51, 1.06
Education						
None		Reference		Reference		Reference
Primary school or above	0.29	0.20, 0.43	0.22	0.14, 0.38	0.41	0.24, 0.68
Pesticide use at home						
No		Reference		Reference		Reference
Yes	0.52	0.39, 0.69	0.49	0.33, 0.72	0.53	0.36, 0.80
History of schistosomiasis						
No		Reference		Reference		Reference
Yes	2.21	1.59, 3.08	1.92	1.26, 2.94	2.22	1.44, 3.43
Age at first pregnancy (years)						
≤18		Reference		Reference		Reference
>18	1.58	1.22, 2.03	1.56	1.12, 2.17	1.66	1.17, 2.34
History of UTI						
No		Reference		Reference		Reference
Yes	1.52	1.12, 2.06	1.20	0.80, 1.80	1.76	1.17, 2.63
ETS exposure						
No		Reference		Reference		Reference
Yes	0.85	0.63, 1.14	0.94	0.64, 1.38	0.79	0.53, 1.17

Note. *OR* = odds ratio; CI = confidence interval; ETS = environmental tobacco smoke; H/HH = husband/head of household; SCC = squamous cell carcinoma; UC = urothelial carcinoma; UTI = urinary tract infection.
*All cases included SCC, UC, and adenocarcinoma.

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Table 3. Adjusted odds ratios and 95% confidence intervals of the associations between living in households with agricultural workers and having bladder cancer among Egyptian women in the two marital status strata.

Predictor variable	All cases*	SCC cases	UC cases
Among unmarried women	*N* = 150	*N* = 67	*N* = 74
H/HH occupation			
Other	Reference	Reference	Reference
Agricultural worker			
OR	0.77	0.82	0.87
95% CI	0.45, 1.32	0.41, 1.64	0.44, 1.70
Among married women	*N* = 218	*N* = 112	*N* = 89
H/HH occupation			
Other	Reference	Reference	Reference
Agricultural worker			
OR	1.54	1.53	1.66
95% CI	1.09, 2.18	0.99, 2.38	1.03, 2.69
Interaction term (Marital status * H/HH occupation)			
p value	.03	.13	.11

Note. OR = odds ratio; CI = confidence interval; H/HH = husband/head of household; SCC = squamous cell carcinoma; UC = urothelial carcinoma. Adjustment was done for education, pesticide use at home, history of schistosomiasis, age at first pregnancy, and the matching variables (age and residence location).
*All cases included SCC, UC, and adenocarcinoma.

When we restricted the analysis to those women who did not work outside the home (387 cases and 719 controls), we obtained similar results.

In the fully adjusted model that included the interaction term (H/HH occupation * marital status) and all cases (Table 3), education, pesticide use at home, history of schistosomiasis, and age at first pregnancy remained significantly associated with bladder cancer risk. The effect of H/HH occupation on bladder cancer in women remained significant in the sensitivity analysis we conducted using multiple imputation.

Comment

We found increased odds of having bladder cancer among women who reported agricultural work as the occupation of their H/HH, but the result was statistically significant only among married women. Increased risk of bladder cancer among agricultural workers has been observed in studies of male[22,24] and female[23] workers, but there is little information in the literature on nonoccupational exposure to agricultural work and bladder cancer risk. Most of the studies addressing cancer risk in agricultural areas involved farm children and childhood cancer,[30,31] and those that addressed women's risk reported associations with other types of cancer,[29,32,33] not bladder. Nonoccupational exposure to hazardous substances related to agricultural work may occur among women whose husbands are farmers or whose family home is located on a farm.[30] Contamination of homes can also occur from drifts during and immediately after pesticide application if the home is located on or near the farm.[30] Agricultural workers themselves can be major contamination sources as they can bring these chemicals into the home on their clothes, shoes, hands, and tools. Pesticide sampling surveys have found traces of these chemicals on clothes, door handles, sink faucets, and telephones after pesticide applications on the family farm.[15,16,37–40] Women and other family members can be exposed when cleaning clothes, from touching objects in the home, or through daily housework.

Our analysis did not measure women's home proximity to a farm or biomarkers of pesticide exposure; however, we did find that women married to agricultural workers had higher odds of bladder cancer than women who were not married and whose head of household (a father, brother, uncle, or son) was an agricultural worker. This difference by marital status suggests that the intimacy of marriage confers a greater degree of exposure to agricultural work than other familial relationships. In a recent review, Deziel et al described several pathways for nonoccupational exposure to pesticides among women living in agricultural areas; they reported that exposures to farming can occur when women in the household perform housekeeping chores such as laundering clothes and vacuuming carpets contaminated with chemicals and solvents used in agricultural work.[30] In an earlier report, Amr et al noted an increased risk of bladder cancer among Egyptian male agricultural workers exposed to pesticides as compared to those not exposed.[14] Therefore, it is plausible that Egyptian women married to agricultural workers have more direct contact with these potential exposures than unmarried women due to a close interaction in sharing the household with their husbands. Future studies are needed to identify specific hazards and/or practices used in Egyptian farming that are associated with bladder cancer risk.

We found that pesticide use at home was not associated with increased bladder cancer risk among women;

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rather, it was associated with significantly decreased risk (*AOR* = 0.59, 95% CI [0.43, 0.81]). We also found this covariate to be highly correlated with education (data not shown), an observation that is consistent with the results of a 2006 study of UK residents, which reported that those with higher incomes, better education, and nonmanual occupations were more likely to use pesticides and weed killers in the home and garden.[41] It is possible that the type, dose, and mode of application of home pest control are quite different from the industrial chemicals sprayed in a large agricultural field, and thus exposure might be different. As previously reported,[42] agricultural workers in Egypt are exposed to a long list of pesticides that include the major categories; presumably they are exposed to a mixture of industrial chemicals.

Another possibility is that women married to agricultural workers are exposed to multiple other hazards including biological contaminants, yet to be investigated, that contribute to the increase in bladder cancer risk. In a household with smokers, exposure to ETS, which we found to be associated with bladder cancer in an earlier study,[13] is a possible contributor to the elevated risk; however, in the present study, we found (1) no statistically significant association between ETS and bladder cancer risk and (2) no change in the main effect when ETS was included in the model. Nonetheless, additive effects of agricultural hazards and secondhand smoke could not be ruled out.

We used data from a large multicenter study of women across Egypt to examine the association between bladder cancer and nonoccupational exposure to agricultural work. The potential for misclassification of disease was minimized as case status was well ascertained by 1 of 2 study pathologists. Using population-based controls, who were frequency matched on age and location to cases, and adjusting for several known risk factors for bladder cancer in this population, including reproductive history, allowed us to minimize selection bias and reduce potential confounding. Nonetheless, the present study has some limitations. Data on the exposure (H/HH occupation) were self-reported by women, and no biological specimens were collected to confirm exposure to pesticides or other chemicals used in farming. One would expect this type of misclassification to be nondifferential. Fifty-one women were missing exposure information in this data set, and we excluded them from the main analyses; however, using multiple imputation techniques, we found that the odds ratio did not change when these women were added to the sample (data not shown). Further, even though female smokers were excluded, residual confounding could exist as women may be hesitant to report this behavior. Misclassification of schistosomiasis history is also possible, which may have biased the associations in unexpected ways. Five percent of the controls and 8% of the cases reported unknown history of schistosomiasis. We conducted a sensitivity analysis that showed no change in the main effect whether women who were unsure of their schistosomiasis history were included in the analysis or not.

These results suggest increased bladder cancer risk among married women whose husbands or heads of household are employed in agricultural work. Future studies to elucidate the mechanism underlying this observation will better inform interventions that would reduce bladder cancer risk among both men and women in Egypt.

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