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Body mass index modifies bladder cancer risk associated with low estrogen exposure among Egyptian women after menopause

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Abstract
Purpose Investigators have reported inconsistent findings regarding associations between body mass index (BMI) and bladder cancer risk, and they have postulated that sex steroids mediate such associations. We assessed the impact of BMI on the relationship between bladder cancer risk and combinations of age at first childbirth, parity, and age at menopause, among Egyptian women.
Methods We used data from our multicenter case–control study of 419 cases and 786 controls in logistic regression models to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of such associations.
Results Age > 18 years at first childbirth and parity ≤ 6 were significantly associated with bladder cancer risk, which was higher when both factors (AOR = 2.31, 95% CI = 1.55–3.43) and age at menopause < 45 years (AOR = 3.51, 95% CI = 1.88–6.55) were present. Early menopause was associated with higher bladder cancer risk in obese (AOR = 2.90, 95% CI = 1.40–5.98) but not normal weight women (AOR = 0.98, 95% CI = 0.58–1.65; $P_{interaction} = 0.11$), and the risk was greatest when both first childbirth at age > 18 years and parity ≤ 6 were present (AOR = 7.60, 95% CI = 1.84–31.35); however, overweight and obesity were associated with significantly lower bladder cancer risk (AOR = 0.59, 95% CI = 0.43–0.81, and AOR = 0.26, 95% CI = 0.18–0.38, respectively).
Conclusion Body mass index appears to modify bladder cancer risk in Egyptian women after menopause by slightly enhancing the risk associated with low estrogen exposure among the obese only. Longitudinal studies of the BMI role in bladder malignancy in this distinctive population are required.

Keywords Bladder cancer · Body mass index · Estrogen exposure · Early menopause · Egyptian women

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Introduction

Urinary bladder cancer is the 9th most common malignancy worldwide, and the disease disproportionately affects more men (~ 75%) than women [1]. Both animal models [2, 3] and human epidemiological studies have explored the role of sex hormones in this disparity, presenting evidence of estrogens [4–7] and anti-androgens [8] as protective factors against this malignancy, particularly the urothelial type.

Investigators have used early age at menarche and/or at first childbirth, late menopause, and parity (number of babies delivered) as proxy indicators of high exposure to estrogens [4–7, 9, 10], and examine their associations with bladder cancer risk; they found inconsistent results. An association between bladder cancer incidence and age at first childbirth was found among Swedish [9] but not among American women [5], and bladder cancer mortality was reported to rise with increasing age at first childbirth among Taiwanese

women [10]. Some investigators found lower bladder cancer risk among parous compared to nulliparous women in the US [7, 11] and in Spain [12], but others reported no significant associations between parity and bladder cancer risk [7, 10]. Similarly, some researchers detected associations between early age at menopause and increased bladder cancer risk [4–6], but not others [12].

On the other hand, increases in body mass index (BMI), used to determine the presence or absence of overweight and obesity, have been reported to be associated with several diseases, including some cancers [13]. Obesity is potentially associated with increased risks of bladder cancer progression and/or mortality [14], based on mixed reports of positive associations [15, 16], while other reports have indicated no correlation [17, 18]. The BMI and cancer risk relationship has been found to differ by population, sex, and ethnic origin [19]. Mechanisms postulated to underlie carcinogenesis [20], and more specifically, bladder cancer development in obese individuals [21], involve sex steroids that also impact reproductive outcomes among women.

In Egypt, urinary bladder carcinomas are diagnosed among women in their fifties and are highly prevalent [6, 22], including both the urothelial (UC) and the squamous cell (SCC) type that is rare in western countries. In a preliminary analysis of data from a case–control study of sex differences in bladder cancer risk factors [6], we found significant associations between estrogen exposure proxies and bladder cancer risk. We conducted the present study of a larger sample of Egyptian women than the preliminary analysis [6] to (1) assess the relationships between bladder cancer risk and a gradient of cumulative estrogen exposure not previously examined, and (2) evaluate the effect of BMI on such associations.

Methods

We analyzed data from our multicenter case–control study conducted in Egypt between 2006 and 2014. The parent study was approved by the institutional review boards of the 3 cancer referral centers (the National Cancer Institute in Cairo, the Oncology Center at Minia University, and the South Egypt Cancer Institute in Assiut), Egypt's Ministry of Health, the University of Maryland, Baltimore, and Georgetown University.

Study population

We previously described the study population in detail [6, 22]. Briefly, cases were recruited from the above-mentioned three cancer referral centers; to be eligible, they had to have been diagnosed with presumed bladder cancer within 12 months and self-identified as capable of completing a 20-min interview. No proxy interviews were conducted. The diagnosis of primary urinary bladder cancer was ascertained by either one of the study's pathologists.

Healthy controls were randomly selected from the general population to frequency match the cases by sex, 5-year age group, governorate (province) of current residence, and urban/rural place of residence.

After cases and controls signed consent forms, trained interviewers administered the in-person questionnaire to collect data on sociodemographic characteristics; environmental exposure histories, including exposure to tobacco smoke; and medical histories, including history of schistosomiasis, weight, and height. Questions for women also asked about reproductive health history, including age at first childbirth, number of babies delivered, menopausal status, and age at menopause.

Variables

The outcome variable was bladder cancer status: all cases, SCC or UC case, or control. The independent variables included (1) age at first childbirth in years, (2) parity (number of babies delivered), and (3) age at menopause in years. Based on the distribution of these variables among the controls (median) and what is known about early versus late menopause, we coded categories as follows: age at first childbirth > 18 years = 1 versus ≤ 18 years = 0; parity ≤ 6 = 1 versus > 6 = 0; and age at menopause < 45 years = 1 versus ≥ 45 years = 0. We used different combinations of these reproductive factors (estrogen exposure proxy variables) to generate two new categorical variables, Composites A and B. As detailed in Table 1, Composite A consisted of level 1 with age at first childbirth ≤ 18 years and parity > 6; level 2, with either one of the level 1 characteristics; and level 3, with age at first childbirth > 18 years and parity ≤ 6. Composite B consisted of level 1, with age at first childbirth ≤ 18 years, parity > 6, and age at menopause ≥ 45 years; level 2, with at least two of the level 1 characteristics; level 3, with at least one of the level 1 characteristics; and level 4, with age at first childbirth > 18 years, parity ≤ 6, and age at menopause < 45 years. Level 1 represented the highest cumulative estrogen exposure for each composite variable and the reference category in the statistical analysis, while levels 3 and 4 represented the lowest cumulative estrogen exposure for Composite A and Composite B, respectively. We used the whole sample to analyze age at first childbirth, parity, and Composite A. For age at menopause and Composite B, we restricted the analyses to only those women who reported menopause.

BMI was calculated for each participant from self-reported weight in kilograms divided by the square of self-reported height in meters. We used the conventional categories of underweight (BMI < 18.5), normal

Table 1 Description of composite variables (and levels) reflecting cumulative estrogen exposure among Egyptian women, based on age (year) at first childbirth, parity (number of babies delivered), and age (year) at menopause

Variable name and level	Age (year) at first childbirth $\leq 18 = 0$ $> 18 = 1$	Parity $> 6 = 0$ $\leq 6 = 1$	Age (year) at menopause $\geq 45 = 0$ $< 45 = 1$	Cumulative estrogen exposure
Composite A (used for the entire study sample)				
Level 1	0	0	NA	Highest[a]
2	0	1	NA	
	1	0	NA	
3	1	1	NA	Lowest
Composite B (used only for the subset who reported menopause)				
Level 1	0	0	0	Highest[a]
2	0	0	1	
	0	1	0	
	1	0	0	
3	1	1	0	
	1	0	1	
	0	1	1	
4	1	1	1	Lowest

[a]The statistical analysis used the highest cumulative estrogen exposure category (Level 1 for each composite variable) as the reference for comparison to each of the other levels

$(18.5 \leq BMI \leq 24.9)$, overweight $(24.9 < BMI \leq 29.9)$, and obese $(BMI > 29.9)$ to describe the study population. Because of the small number of underweight participants, we combined them with those of normal weight and used BMI as a tri-level categorical variable, with normal as the reference.

Other examined covariates included (1) marital status, regrouped as currently married versus all other categories (never married, widowed, separated, or divorced); (2) education (some versus none); (3) history of schistosomiasis (yes versus no); (4) environmental tobacco smoke (ETS) (exposure either in or outside the home versus none); and (5) the matching variables (age and residence location). Only 14 cases and 14 controls reported smoking cigarettes, water pipes, or both; therefore, we restricted the analyses to women who never smoked.

Statistical analyses

We used *t* test and Chi-square statistics for continuous and categorical variables, respectively, to compare cases to controls. We used unconditional logistic regression models of the associations between each variable and bladder cancer risk to estimate unadjusted (OR) and adjusted (AOR) odds ratios with 95% confidence intervals (CIs).

We tested any variable that was significantly associated with the outcome (p value ≤ 0.05) for its potential effect modification or confounding of the association between cancer and each of the estrogen exposure proxies. Using a stepwise approach, we built multivariable unconditional logistic regression models including covariates that remained significantly associated with the outcome or modified the regression coefficient of the main effect by $\geq 10\%$.

We looked for effect modification by adding each main predictor variable, one covariate, and the interaction term for the two to the model one at a time and testing for its statistical significance. We also conducted analyses after stratification by the potential modifier.

The final models included significant covariates and the matching variables, age, and area of residence (North versus South and urban versus rural). We also conducted separate analyses of all cases, SCC cases, and UC cases. We used SAS version 9.4 software (SAS Institute, Cary, NC, USA) to conduct all statistical analyses.

Results

The study sample consisted of 433 cases (200 SCC, 187 UC, and 46 adenocarcinoma) and 800 controls. The mean ages for cases and controls were 56.1 years and 54.4 years, respectively (Table 2). Most participants were not educated and lived in rural areas in south Egypt. More cases than controls had a first child at age > 18 years (53% versus 42%), had ≤ 6 children (this study population's median) (66% versus 63%), and reached menopause at age < 45 years (34% versus 27%) (Table 3). More controls than cases had high BMI (> 24.9); thus, they were overweight or obese (~ 70% versus 49%). More cases (23%) than controls (11%) reported history of schistosomiasis.

For the rest of the analyses we used 419 cases and 786 controls, all of whom never smoked. Table 4 depicts the unadjusted and adjusted associations between bladder cancer risk and different proxies of estrogen exposure. The odds of having bladder cancer were significantly high for women aged > 18 years at first childbirth and those aged < 45 years at menopause, and high but not statistically significantly for those who had ≤ 6 children. The combination of either two (Composite A) or all three (Composite B) of these variables, which represented proxies for cumulative estrogen exposure, revealed significant positive trends ($p < 0.05$) for higher bladder cancer risk with lower cumulative estrogen exposure (Table 4).

BMI was inversely associated with bladder cancer risk. Compared to normal weight women, those overweight and obese women had lower odds of having bladder cancer (OR = 0.58, 95% CI = 0.43–0.78, and OR = 0.26, 95% CI = 0.19–0.36, respectively).

Among the other covariates assessed, schistosomiasis history (OR = 2.27, 95% CI = 1.64–3.13), education (OR = 0.32,

Table 2 Sociodemographic Variables among Egyptian Women Controls Compared to Urinary Bladder Cancer Cases

Variable	Controls n = 800 n (%)	All[a] cases n = 433 n (%)	p value	SCC[b] cases n = 200 n (%)	p value	UC[c] cases n = 187 n (%)	p value
Age (SD) (year)	54.4 (12.2)	56.1 (11.2)	**0.02**	53.2 (10.7)	0.19	59.3 (10.7)	**< 0.0001**
Age group							
≤ 45	209 (26.1)	80 (18.5)	**0.01**	46 (23.0)	**0.002**	21 (11.2)	**< 0.0001**
> 45 to ≤ 55	221 (27.6)	136 (31.4)		82 (41.0)		43 (23.0)	
> 55 to ≤ 65	238 (29.8)	130 (30.0)		48 (24.0)		69 (36.9)	
> 65	132 (16.5)	87 (20.1)		25 (12.0)		54 (28.9)	
Education							
None	593 (74.3)	389 (89.8)	**< 0.0001**	183 (91.5)	**< 0.0001**	166 (88.8)	**< 0.0001**
Some	205 (25.7)	44 (10.2)		17 (8.5)		21 (11.2)	
Residence							
North	80 (10.0)	57 (13.2)	0.09	24 (12.0)	0.4	26 (13.9)	0.12
South	720 (90.0)	376 (86.8)		176 (88.0)		161 (86.1)	
Urban	100 (12.5)	55 (12.7)	0.91	20 (10.0)	0.3	31 (16.6)	0.13
Rural	700 (87.5)	378 (87.3)		180 (90.0)		156 (83.4)	
Marital status							
Never married	10 (1.2)	9 (2.1)	**0.003**	7 (3.5)	**0.006**	1 (0.5)	**0.004**
Married	538 (67.3)	252 (58.2)		119 (59.5)		102 (54.6)	
Widowed	241 (30.1)	157 (36.2)		66 (33.0)		79 (42.2)	
Divorced	11 (1.4)	15 (3.5)		8 (4.0)		5 (2.7)	
Smoking							
Never	786 (98.2)	419 (96.8)	0.06	103 (96.5)	0.14	182 (97.3)	0.14
Water pipe	11 (1.4)	6 (1.4)		4 (2.0)		2 (1.1)	
Cigarettes	3 (0.4)	7 (1.6)		3 (1.5)		3 (1.6)	
Both	0	1 (0.2)		0		0	
ETS[d]							
No	328 (41.0)	184 (42.5)	0.6	76 (38.0)	0.4	89 (47.6)	0.1
Yes	472 (59.0)	249 (57.5)		124 (62.0)		98 (52.4)	

Boldface indicates statistical significance

[a] All cases included SCC, UC, and adenocarcinoma

[b] Squamous cell carcinoma

[c] Urothelial cell carcinoma

[d] Environmental tobacco smoke; because of missing data, the sum of the n in each column may not add to the total

95% CI = 0.22–0.46), and marital status (OR = 0.64, 95% CI = 0.50–0.82) were significantly associated with bladder cancer risk.

After adjustment for the matching variables (age and residence location), as well as the covariates listed above, including the categorical BMI, the positive trend in the associations between low cumulative estrogen exposure proxies and bladder cancer risk remained for all cases, as well as for the SCC and the UC types (Table 4). Indeed, the Composite B combination variable, level 4, with age at menopause < 45 years, age at first childbirth > 18 years, and parity ≤ 6, was significantly associated with higher bladder cancer risk than each factor separately (AOR = 3.51, 95% CI = 1.88–6.55) (Table 4). Analyses conducted separately for SCC and UC revealed similar patterns, except the risk

for those with the lowest estrogen exposure that was slightly higher for UC than SCC (AOR = 4.84, 95% CI = 1.97–11.89, and AOR = 2.85, 95% CI = 1.25–6.50, respectively) (Table 4). Furthermore, the significant unadjusted OR (95% CI) [1.44 (1.08–1.93)] for early menopause became statistically non-significant [1.29 (0.92–1.81)] after adjustment for covariates, specifically the BMI categories.

In the fully adjusted models of the whole study sample, the AORs (95% CIs) were 0.59 (0.43–0.81) for overweight and 0.26 (0.18–0.38) for obese: not different from the unadjusted ORs. None of the interaction terms was statistically significant when introduced into the model. We then conducted logistic regression analyses after stratification of the study sample by BMI level (Table 5). Bladder cancer risks associated with age at first childbirth and with parity were

Table 3 Health and endogenous estrogen exposure variables among Egyptian women controls compared to urinary bladder cancer cases

Variable	Controls n = 786 n (%)	All[a] cases n = 419 n (%)	p value	SCC[b] cases n = 193 n (%)	p value	UC[c] cases n = 182 n (%)	p value
Age at first childbirth, years							
≤ 18	463 (57.9)	201 (46.4)	**0.0001**	92 (46.0)	**0.002**	86 (46.0)	**0.003**
> 18	337 (42.1)	232 (53.6)		108 (54.0)		101 (54.0)	
Parity n (%), children							
> 6	293 (36.6)	145 (33.5)	0.2	65 (32.5)	0.2	64 (34.2)	0.5
≤ 6	507 (63.4)	288 (66.5)		135 (67.5)		123 (65.8)	
Menopause							
No	249 (31.2)	56 (12.9)	**< 0.0001**	32 (16.0)	**< 0.0001**	15 (8.0)	**< 0.0001**
Yes	550 (68.8)	377 (87.1)		168 (84.0)		172 (92.0)	
Age at menopause, years[d]							
≥ 45	402 (73.1)	246 (65.2)	**0.01**	107 (63.7)	**0.01**	113 (65.7)	0.06
< 45	148 (26.9)	131 (34.7)		61 (36.3)		59 (34.3)	
BMI continuous	28.7 (6.2)	25.0 (5.2)	**< 0.0001**	24.7 (4.7)	**< 0.0001**	25.3 (5.8)	**< 0.0001**
< 18.5	21 (2.8)	27 (6.9)	**< 0.0001**	14 (7.7)	**< 0.0001**	12 (7.1)	**< 0.0001**
≥ 18.5 to ≤ 24.9	202 (27.3)	172 (44.0)		78 (42.8)		71 (42.3)	
> 24.9 to ≤ 29.9	235 (31.8)	125 (32.0)		62 (34.1)		52 (30.9)	
> 29.9	281 (38.1)	67 (17.1)		28 (15.4)		33 (19.7)	
History of schistosomiasis							
No	661 (82.6)	301 (69.5)	**< 0.0001**	139 (69.5)	**0.0002**	134 (71.7)	**0.0008**
Yes	93 (11.6)	100 (23.1)		42 (21.0)		41 (21.9)	
Unknown	46 (5.8)	32 (7.4)		19 (9.5)		12 (6.4)	
Composite A[e] level							
1	206 (25.8)	82 (18.9)	**0.005**	39 (19.5)	**0.02**	33 (17.7)	**0.05**
2	344 (43.0)	182 (42.0)		79 (39.5)		84 (44.9)	
3	250 (31.2)	169 (39.1)		83 (41.0)		70 (37.4)	
Composite B[d,e] level							
1	122 (22.2)	44 (11.7)	**0.0001**	21 (12.5)	**0.0005**	16 (9.3)	**0.001**
2	214 (38.9)	134 (35.5)		54 (32.1)		68 (39.5)	
3	166 (30.2)	146 (38.7)		66 (39.3)		67 (40.0)	
4	48 (8.7)	53 (14.1)		27 (16.1)		21 (12.2)	

Boldface indicates statistical significance

[a] All cases included SCC, UC, and adenocarcinoma

[b] Squamous cell carcinoma

[c] Urothelial cell carcinoma

[d] Analysis among women who reported menopause

[e] Composite A and Composite B used different combinations of the three endogenous estrogen exposure variables (age at first birth, parity, and age at menopause), with level 1 representing the highest endogenous estrogen exposure for either variable, while levels 3 and 4 represented the lowest for Composites A and B, respectively (see Table 1 for details)

not significantly different among the normal weight, overweight, and obese BMI strata. However, menopause at age < 45 years was significantly associated with higher bladder cancer risk in obese (AOR = 2.90, 95% CI = 1.40–5.98), but not normal weight group (AOR = 0.98, 95% CI = 0.58–1.65; $P_{interaction}$ = 0.11), and the risk was greatest when both first childbirth at age > 18 years and parity ≤ 6 were present (AOR = 7.60, 95% CI = 1.84–31.35) (Table 5); however, overweight and obesity were associated with significantly

lower bladder cancer risk (AOR = 0.59, 95% CI = 0.43–0.81, and AOR = 0.26, 95% CI = 0.18–0.38, respectively).

To further understand the contribution of the BMI to the postmenopausal risk of bladder cancer, we conducted regression analyses of the BMI categories restricted to menopaused women, before and after stratification by age at menopause. As shown in Table 6 and in the analyses of the whole sample, the higher the BMI, the lower the risk; however, the statistically significant lower risk (AOR = 0.58,

Table 4 Unadjusted and adjusted associations between single and composite reproductive health variables and urinary bladder cancer risk among Egyptian women

Variable	All[a] cases		SCC[b] cases		UC[c] cases	
	Unadjusted OR (95% CI)[d]	Adjusted[e] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at first childbirth, years						
≤ 18	Ref	Ref	Ref	Ref	Ref	Ref
> 18	**1.56 (1.23–1.98)**	**1.76 (1.33–2.33)**	**1.57 (1.15–2.16)**	**1.87 (1.29–2.71)**	**1.60 (1.16–2.21)**	**1.71 (1.18–2.49)**
Parity, childern						
> 6	Ref	Ref	Ref	Ref	Ref	Ref
≤ 6	1.23 (0.95–1.59)	**1.44 (1.07–1.94)**	1.18 (0.85–1.66)	1.36 (0.91–2.03)	1.17 (0.83–1.64)	**1.52 (1.02–2.28)**
Age at menopause, years[f]						
≥ 45	Ref	Ref	Ref	Ref	Ref	Ref
< 45	**1.44 (1.08–1.93)**	1.29 (0.92–1.81)	**1.58 (1.09–2.29)**	1.12 (0.71–1.78)	1.39 (0.96–2.02)	1.40 (0.91–2.15)
Composite A[e]						
Level 1	Ref	Ref	ref	Ref	Ref	Ref
2	1.37 (0.99–1.88)	**1.56 (1.07–2.28)**	1.22 (0,80-1.87)	1.37 (0.82–2.29)	1.60 (1.02–2.50)	**1.92 (1.13–3.25)**
3	**1.73 (1.25–2.40)**	**2.31 (1.55–3.43)**	**1.69 (1.10–2.59)**	**2.25 (1.33–3.80)**	1.83 (1.15–2.91)	**2.51 (1.45–4.36)**
p value for trend	*0.001*					
Composite B[f,g]						
Level 1	Ref	Ref	Ref	Ref	Ref	Ref
2	**1.74 (1.16–2.63)**	**1.85 (1.14–3.01)**	1.44 (0.83–2.51)	1.51 (0.77–2.97)	**2.60 (1.42–4.75)**	**3.04 (1.47–6.29)**
3	**2.40 (1.58–3.63)**	**2.67 (1.62–4.38)**	**2.19 (1.27–3.79)**	**2.33 (1.10–4.59)**	**3.17 (1.72–5.82)**	**3.78 (1.80–7.94)**
4	**3.24 (1.91–5.49)**	**3.51 (1.88–6.55)**	**3.38 (1.74–6.57)**	**2.85 (1.25–6.50)**	**3.68 (1.75–7.75)**	**4.84 (1.97–11.89)**
p value for trend	*0.003*					

Boldface indicates statistical significance

[a]All cases included SCC, UC, and adenocarcinoma

[b]Squamous cell carcinoma

[c]Urothelial cell carcinoma

[d]Odds ratio (95% confidence interval)

[e]Adjusted for matching variables (age and residence location), BMI, history of schistosomiasis, education, and marital status

[f]Analysis among women who reported having reached menopause; Composite A and Composite B used different combinations of the three endogenous estrogen exposure variables (age at first childbirth, parity, and age at menopause), with level 1 representing the highest endogenous estrogen exposure for either variable, while levels 3 and 4 represented the lowest for Composites A and B, respectively (see Table 1 for details)

95% CI = 0.43–0.78) among the overweight subgroup of the whole sample increased and became borderline significant in the sample restricted to menopaused women (AOR = 0.71, 95% CI = 0.50–1.01) (Table 6). Furthermore, we noted significantly low AORs for both overweight and obese categories in the age at menopause ≥ 45 years stratum, while we found no significant effect in the age at menopause < 45 years stratum (Table 6).

Discussion

Our current study is the first to examine the impact of cumulative endogenous estrogen exposures by BMI level on bladder cancer risk among postmenopausal women. We found significant dose–response associations between bladder cancer risk and indicators of cumulative endogenous estrogen exposure (age at first childbirth, parity, and age at menopause) in Egyptian women; the lower the exposure, the higher the risk. We also found BMI to be significantly inversely associated with bladder cancer risk independently of the other variables included in the regression models; however, the BMI effect appeared to be slightly attenuated among menopaused women (Table 6) and to modify the risk associated with early menopause. Indeed, we found greater odds of having bladder cancer for obese (BMI > 29.9) (AOR = 2.90, 95% CI = 1.40–5.98) than for normal weight (AOR = 0.98, 95% CI = 0.58–1.65) women with early menopause.

Our findings differ from the results of a dose–response meta-analysis, which suggested a non-linear positive association between BMI and bladder cancer risk based on

Table 5 Adjusted associations between single and composite reproductive health variables and urinary bladder cancer risk among Egyptian women after stratification by different categories of body mass index (BMI)

Variable	Adjusted[a] odds ratio (95% confidence interval)		
	BMI ≤ 24.9	24.9 < BMI ≤ 29.9	BMI > 29.9
Age at first childbirth, years			
≤ 18	Ref	Ref	Ref
> 18	**2.01 (1.30–3.11)**	1.55 (0.95–2.52)	**1.87 (1.03–3.39)**
Parity, children			
> 6	Ref	Ref	Ref
≤ 6	1.56 (0.99–2.45)	1.16 (0.69–1.96)	1.83 (0.93–3.58)
Age at menopause, years[b]			
≥ 45	Ref	Ref	Ref
< 45	0.98 (0.58–1.65)	1.19 (0.65–2.17)	**2.90 (1.40–5.98)**
Age at menopause*BMI interaction term			
p value		*0.76*	*0.11*
Composite A[c] level			
1	Ref	Ref	Ref
2	1.44 (0.81–2.57)	1.69 (0.88–3.24)	1.62 (0.69–3.80)
3	**2.78 (1.50–5.14)**	1.79 (0.90–3.55)	**2.84 (1.20–6.75)**
Composite B[b,c] level			
1	Ref	Ref	Ref
2	1.80 (0.86–3.77)	1.88 (0.81–4.37)	2.47 (0.75–8.13)
3	**2.14 (1.02–4.50)**	**2.71 (1.11–6.60)**	**4.49 (1.38–14.58)**
4	**3.51 (1.32–9.35)**	2.85 (0.98–8.32)	**7.60 (1.84–31.35)**

Boldface indicates statistical significance

[a] Adjusted for matching variables (age and residence location), schistosomiasis history, education, and marital status

[b] Analysis among women who reported having reached menopause

[c] Composite A and Composite B were generated using different combinations of the three endogenous estrogen exposure variables (age at first childbirth, parity, and age at menopause), with level 1 representing the highest endogenous estrogen exposure for either variable, while levels 3 and 4 represented the lowest for Composites A and B, respectively (see Table 1 for details)

Table 6 Associations between BMI categories and bladder cancer risk among menopaused women before and after stratification by age at menopause

BMI	All menopaused women			Menopause at ≥ 45 years		Menopause at < 45 years	
	Case/control *n*	Unadjusted OR[a] (95% CI)	AOR[b] (95% CI)	Case/control *n*	AOR (95% CI)	Case/control *n*	AOR (95% CI)
≤ 24.9	167/169	Ref	Ref	118/118	Ref	49/51	Ref
> 24.9 to ≤ 29.9	106/148	0.72 (0.52–1.01)	0.71 (0.50–1.01)	70/108	**0.64 (0.42–0.98)**	36/40	0.91 (0.47–1.74)
> 29.9	55/195	**0.28 (0.20–0.41)**	**0.26 (0.17–0.40)**	31/148	**0.19 (0.11–0.32)**	24/47	0.50 (0.24–1.03)

Boldface indicates statistical significance

[a] Odds ratio and 95% confidence interval

[b] Adjusted for matching variables (age and residence location), schistosomiasis history, education, and marital status

14 prospective studies [23]. Although the meta-analysis authors explored biologic mechanisms contributing to the association between excess weight and cancer risk, including possible increased bioavailability of steroid hormones, they did not address sex differences and impact on risk from endogenous estrogen exposures. Our results also diverge from those of Cantiello et al. [18], who conducted a systematic review examining metabolic syndrome and each of its components separately (high blood pressure, obesity, and diabetes) in relation to bladder cancer risk, and reported equivocal findings; they also did not consider the impact of the assessed risk factors among women at different life stages. Further, a systematic review [14] based on 31 investigations that included diverse designs

found a potential association of obesity and increased bladder cancer risk, as well as increased risk of recurrence and mortality; the authors acknowledged that sex disparities in bladder cancer may involve obesity-linked hormonal changes, considering estrogen production by adipose tissue [24] and evidence of estrogen receptors in bladder cancer tissues [25, 26]. In postmenopausal women, adipose tissue is the main source of circulating estrogen [24]; and an increase in BMI was reported to be associated with a decrease in estradiol concentrations in premenopausal women but an increase in postmenopausal women [27]. Therefore, one would expect obesity to counteract the effect of early menopause on bladder cancer risk, which was not the case in our study. The effect of early menopause (OR = 1.44, 95% CI = 1.08–1.93) was attenuated after adjustment for covariates driven by BMI categories (AOR = 1.29, 95% CI = 0.92–1.81) (Table 4), but in the stratified analysis by BMI, the AORs were significantly higher (AOR = 2.90, 95% CI = 1.40–5.98) among obese than among normal weight women (AOR = 0.98, 95% CI = 0.58–1.65). It is possible that in postmenopausal women, sex steroids, including estrogen, are produced and metabolized in target tissues; they do not function as the circulating hormones, and hence, their involvement in the development of metabolic syndrome [28]. Our finding that obese women (BMI > 29.9) with menopause at age < 45 years or with overall low cumulative estrogen exposure had higher odds of bladder cancer than those of normal weight further raises the question of the roles of different types of estrogen (estradiol, estrone, or estriol) and other sex steroids in bladder cancer risk.

Although we used BMI at the time of diagnosis, our findings of an inverse association between BMI and bladder cancer risk were consistent with findings from longitudinal studies of BMI and other cancers. In a prospective pooled analysis of two large Nurses' Health Study cohorts, significant inverse associations were found between BMI at age 18 years and during childhood, and risk of most subtypes of breast cancer [29]. A recent multicenter analysis of pooled individual-level data from 758,592 premenopausal women, aged 18 to 54 years, from 19 prospective cohorts of breast cancer, found increased adiposity to be associated with a reduced risk of premenopausal breast cancer, and the strongest inverse associations were observed for BMI in early adulthood [30].

The present study relied on self-reported reproductive history for the endogenous estrogen exposures and for the height and weight used to calculate BMI; therefore, potential for bias exists. Tendencies for self-reported height to be overestimated and weight underestimated compared to measured values would potentially lead to bias that is greater among overweight and obese participants than those of normal weight; such biases in our study would result in an underestimation of our finding.

Where potential for bias remains, we believe that non-differential versus differential recall error between cases and controls is more likely. The women in our study were unlikely to be biased by knowledge of previous research findings on possible associations of bladder cancer with the examined risk factors.

While assessing the impact of endogenous estrogen exposures on bladder cancer risk by BMI from a single point in time could be problematic because of the uncertain exposure window of relevance, our findings nevertheless suggest the need for further studies to determine preventive potential, whether related to BMI as a marker of hormonal activity suppressive of malignancy, better nutrition, or immune function, or other protective factors in early life or at other points in the life course.

Nonetheless, our study addressed BMI and reproductive health variables in a population that is distinct from other previously studied populations; Egyptian women had their first babies at relatively early ages (median 18 years) and for some as early as 12 years; and the median number of born babies was 6. The cases were diagnosed with bladder cancer in their fifties, and nearly half were SCC and not the UC type reported predominantly in western countries. Our finding that obesity (BMI > 29.9) enhanced the association between bladder cancer risk and low cumulative estrogen exposure in postmenopausal women with distinctive characteristics is novel and supports the need for longitudinal studies of BMI, reproductive factors, and cancer risk among different populations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The institutional review boards of the 3 cancer referral centers (the National Cancer Institute in Cairo, the Oncology Center at Minia University, and the South Egypt Cancer Institute in Assiut), Egypt's Ministry of Health, the University of Maryland, Baltimore, and Georgetown University approved the protocols.

Informed consent Written informed consent was obtained from all participants.

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