Bladder cancer and reproductive factors among women in Spain

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Abstract

Hormonal factors, possibly related to reproductive characteristics, may play a role in the risk of bladder cancer among women. To study this, we investigated the effects of reproductive factors on female bladder cancer risk. Information on reproductive and other risk factors was gathered in personal interviews from 152 female cases and 166 matched controls from 18 hospitals in five regions of Spain during 1998–2001. Logistic regression was used to estimate the association between bladder cancer and reproductive factors, including ever-parous status, age at first live birth, age at last live birth, age at menarche, age at menopause, menopausal status, and duration of menstruation. After adjustment for age, smoking, and high-risk occupation, ever-parous women were at decreased risk relative to nulliparous women (odds ratio = 0.43, 95% confidence interval =

0.21–0.87). There was no consistent pattern in risk with the age- or duration-related reproductive factors (e.g., age at first live birth, age at last live birth, age at menarche, age at menopause, menopausal status, and duration of menstruation) that we evaluated. Women have a lower risk of bladder cancer than men, and hormonal factors related to childbearing may play a role.

Keywords

Bladder cancer; Reproductive factors; Ever-parous; Women

Introduction

In 2007, bladder cancer was diagnosed in ~67,000 persons in the United States, making it the fourth most common cancer in the United States [1]. Among worldwide populations covered by cancer registries reporting to the International Agency for Research on Cancer, 356,557 cases were reported in 2002, the ninth most common cancer [2]. In some studies, bladder cancer was associated with female reproductive factors such as number of live births, age at menopause, menopausal status, and hormone replacement therapy, raising the possibility that hormonal factors may also be related to etiology [3–6]. However, other studies did not find significant results [7–9]. The objective of the current analysis was to further investigate the effects of reproductive factors on bladder cancer risk among Spanish women.

Materials and methods

This study was part of a larger investigation, the Spanish Bladder Cancer Study that included men and women. Methods for the overall study are described by Samanic et al. [30]. In this part of the study, we identified 179 female cases from 18 hospitals in five regions of Spain (Barcelona, Valles, Asturias, Alicante, and Tenerife) during 1998–2001. Of these, 152 (85%) agreed to participate in the study and were interviewed. Cases were all patients with newly diagnosed urothelial carcinoma of the urinary bladder (*International Classification of Diseases, Ninth Edition code* 1880–1889) including carcinoma in situ (*International Classification of Diseases, Ninth Edition code* 2337) of the bladder, ureteric orifice and urachus, who were aged 21–80 years at the time of diagnosis and resided in the catchment areas of the participating hospitals. For each presumptive bladder cancer case, one control was selected by matching age (within 5 years), gender, race/ethnicity, and hospital. Eligible controls were patients admitted to the same hospital around the same time as the cases for diseases/conditions not recognized to be associated with bladder cancer risk (40% fracture, 21% hernia of abdominal cavity, 9% intestinal obstruction without mention of hernia, 7% disease of veins and lymphatics, and other diseases of the circulatory system, 4% infections of skin and subcutaneous tissue, 6% open wound of limb, 4% acquired deformities of toe, 2% appendicitis, 2% elective surgery for other purposes, 2% dislocation, and 5% other diagnosis). We identified 185 female controls and 166 (90%) of them agreed to participate in the study and to be interviewed. The age range of cases and controls was 33–80 years. This study was approved by the Institutional Review Board of National Cancer Institute, the Institut Municipal d'Investigacio Medica, and the ethics committees of all participating hospitals.

After obtaining written informed consent, a structured interview was conducted by computer-assisted trained interviewers (CATI). Questionnaire topics included demographic characteristics (age, race, education, marital status, income level), height, usual adult weight, details of tobacco use (former/current status, frequency, duration, amount, tobacco type), lifetime occupational history, dietary intake, and reproductive factors (i.e., ever-parous, age

at first live birth, age at last live birth, age at menarche, age at last menstrual period, date/year of last menstrual period, regular menstrual periods). Duration of menstruation was calculated from age at menarche to the date/year of the last menstrual period. Menopausal status was derived from information regarding regular menstrual periods, age at last menstrual period, and date and year of last menstrual period. In our analysis, data on the reproductive factors were stratified into logical categories. The cut-point for age at menopause (<47, 47–51, and ≥52 years) was based on the distribution of age and the mean age of menopause (48.5 years) among study controls. All female subjects were white.

We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) associated with reproductive factors and risk of bladder cancer. In developing regression models, all potential risk factors were tested for confounding. If the potential confounding factor was not significantly related ($p < 0.05$) to cancer risk or its absence in the regression model did not change the odds ratio by more than 10%, we did not consider it to be a confounder and it was not included in the multivariate model. The OR and 95% CI to evaluate the relationship between reproductive factors and bladder cancer were adjusted for age at diagnosis/interview (continuous), tobacco use (ever/never smoking), and ever employed in high-risk occupations for bladder cancer, three well-established risk factors. The definition of high-risk occupations was based on professional judgment and the literature [10,11]. The high-risk industries included general building contractors, heavy construction contractors, heavy construction except for highway, yarn and thread mills, and miscellaneous textile goods. The high-risk occupations included painters; paperhangers; plasterers; truck drivers and tractor-trailers; railroad brake, signal, and switch operators; sailors and deckhands; precision laundering, cleaning, and dyeing occupations; textile machine setup operators, and welders; and solders. In addition to ever/never smoking, all ORs for reproductive factors were tested by adjustment for more refined measures of smoking: never/former/current cigarette smoking, smoking frequency (nonsmoker, occasional, and regular smoker), smoking duration (nonsmoker, <30, and 30+ years), and smoking amount (nonsmoker, 0–14, and >14 pack-years). We estimated the *p* value for trend for all reproductive factors using the median value of age- and duration-related variables.

Results

Table 1 describes characteristics of the 152 cases and 166 controls in this study. Bladder cancer cases had a higher percentage of high-risk occupations, a higher percentage of current smokers, and a lower percentage of ever-parous women than controls.

We found a significant positive trend in risk with increasing duration, frequency, and daily amount of smoking, consistent with the findings of Samanic et al. [30]. Marital status, education, income, BMI, and fruit and vegetable intake level were not related to bladder cancer risk in this population, after adjustment for smoking frequency, age, and high-risk occupation (data not shown).

Relative to nulliparous women, parous women had an OR of 0.43 (95% CI = 0.2–0.9), after adjustment for age, smoking status, and high-risk occupation (Table 2). Among never-smokers, being parous showed a similar protective effect (OR = 0.39, 95% CI = 0.2–0.8). Among the 20 cases and 11 controls who were former or current smokers, the OR for ever-parous status was 0.62 (95% CI = 0.1–3.2). However, the number of smokers was very small and the OR was imprecise. The relationship between female bladder cancer and ever-parous status was not confounded by other potential risk factors such as region, income, education, marital status, body mass index (BMI), or vegetable and fruit intake.

In addition to ever-parous status, other reproductive factors (age at first live birth, age at last live birth, age at menarche, age at menopause, menopausal status, and duration of menstruation) were not statistically related to bladder cancer risk, either among all women or ever-parous women (Table 3). There was no consistent trend in risk with age at first live birth, age at last live birth, age at menarche, age at menopause, or duration of menstruation. The study population mainly consisted of postmenopausal women (87.5% of cases and 90.1% of controls). Table 3 shows that menopausal status was not significantly related to bladder cancer risk among all female subjects or among ever-parous female subjects. Adjustment with more refined measures of smoking (e.g., smoking frequency, duration, intensity) did not materially alter the strength of observed associations. Additional adjustment for region in the logistic regression model did not change the relationship between reproductive factors and bladder cancer risk.

Discussion

In this study, being ever-parous was significantly associated with decreased risk of female bladder cancer, after adjustment for age, tobacco use, and high-risk occupation. Several studies [3–9] have investigated the association between reproductive factors and bladder cancer risk. Among these, only two U.S. studies investigated the relationship between ever-parous status and bladder cancer [3,4]. Our study replicated, in a Spanish population, findings from a case–control study in Iowa [3]. A U.S. cohort study found a nonsignificant decreased risk of being ever-parous for bladder cancer [4]. Other studies, conducted in the United States, Slovakia, and Italy investigated number of live births (usually as contrasted with being nulliparous) and pointed in the same direction [4–9]. In these studies, having one or more live births was associated with decreased risk of bladder cancer; however, after birth of the first child, an increase in the number of live births did not appear to influence bladder cancer risk. None of these latter studies estimated the effect of ever-parous status.

Cohort and case–control studies provide inconsistent results for the effect of age at menopause. Prizment et al. [6] and McGrath et al. [4] indicated that women whose age at menopause was younger than 47 and 45 years, respectively, were at elevated risk. However, Pelucchi et al. [5] showed higher risk among women whose age of menopause was above 49 years, but the association was not significant. Here, we used age at menopause between 47 and 51 years as the referent. We found lower risks when menopause occurred at either younger or older ages; however, the 95% CI for the reduced OR (0.70 and 0.58) included 1.0 in both instances. Previous case–control and cohort studies did not have consistent results for other reproductive factors, including age at first birth, age at last birth, age at menarche, age at menopause, menopausal status, hormone replacement therapy use, and oral contraceptives.

During pregnancy, estrogen and progesterone levels increase substantially [12–15]. These higher levels change bladder dynamics to increase bladder capacity and compliance [16,17]. Estrogen and progesterone receptors (ERs and PRs) that mediate these responses are found in normal human female bladder tissue, bladder cell carcinomas, and bladder tumors [18–21]. Estrogen stimulates cellular proliferation in the female lower urinary tract, but this action is not found in the dome and trigone of the bladder [22]. Estradiol can moderately stimulate bladder cancer cell growth in vitro, and antiestrogens such as 4-hydroxytam-oxifen and raloxifene have a strong inhibitory effect on growth of bladder tumor cell lines [23]. Estrogen and progesterone have an antagonistic effect on human cells, and it is likely that their major increases during pregnancy have profound effects on bladder physiology. Batra and Iosif [12] suggested that progesterone results in the suppression of estrogen receptor during pregnancy. These studies indicate that estrogen may increase bladder cancer risk, but progesterone may decrease the risk through suppressing ER. The substantial increased levels

of estrogen and progesterone during pregnancy may play a role in decreased risk of bladder cancer for women.

Androgens, precursors in the production of estrogen, might also be related to the risk of bladder cancer in women [15]. Androgen receptors (ARs) have been found in normal bladder epithelium of rats and humans [24,25], and in both male and female patients' bladder carcinomas [26,27]. Using a chemical carcinogen (*N*-butyl-*N*-(4-hydrox-ybutyl) nitrosamine) to induce bladder cancer in mice, Miyamoto et al. [28] found that androgen increased the growth of AR-positive bladder cancer cells and that androgen depletion and/or antiandrogen treatment suppressed cancer progression. Their results indicated that proliferation of some bladder cancers is androgen sensitive.

In most populations, the bladder cancer incidence rate among men is 3–5 times higher than that in women [11]. Reasons for this differential are not completely understood; however, the male excess can be partially explained by higher smoking rates and elevated exposure to occupational carcinogens. After accounting for gender differences in these risk factors in a large study from the United States, the incidence of bladder cancer for men was still 2.7 times higher than that in women [29]. In the Spanish Bladder Cancer Study, most of the male excess was explained by smoking, with the male/female incidence ratio being 1.7 after accounting for smoking [30]. Our findings of possible hormonal influence on risk suggest a mechanism for the observed excess of bladder cancer among men.

This study has several strengths. Although this is a hospital-based investigation, almost all newly diagnosed bladder cancer cases residing in catchment areas of participating hospitals are treated locally, and it is likely that we enlisted almost all newly diagnosed bladder cancer cases that occurred in covered populations. Response rates for cases and controls were excellent. This is the first study to estimate risk of bladder cancer associated with reproductive factors in a Spanish population, whose risk difference of bladder cancer incidence due to gender exists (1.7) after eliminating the effect of cigarette smoking [30]. Information was available on well-known confounders including age, cigarette smoking, and high-risk occupations, and appropriate adjustments were made. It is unlikely that recall bias played an important role in this case–control study because the reproductive factors that we considered, such as having a live child or not, age at menarche, age at first live birth, age at last live birth, and age at menopause, are usually important events in women's lives. Lastly, 70% of the study subjects were women who had never smoked, so we were able to minimize the potential confounding effects of smoking in our analyses.

Among the limitations of this study, there was relatively small number of female bladder cancer cases (152 women). Few women had ever smoked, and we could not estimate the effect of tobacco use on the risk associated with reproductive factors. Information on the number of live births, hormonal replacement therapy, and oral contraceptives was not available, so we could not estimate the risks associated with these factors. As noted, we used hospitalized patients as controls, with the possibility that selection bias may have operated. We evaluated this possibility. The majority (40%) of the female control group was selected from patients with any kind of fracture. The single most common was fracture of the neck of the femur, about 13% of the female control group. Since being parous in our study was found to have a significant association with bladder cancer risk, we tested the relationship among controls between being parous, and having had any kind of fracture or hip-fracture, and found no association with either (p = 0.51 and 0.23 respectively). One of the limitations is the missing information for some reproductive factors in this study. In order to test whether missing values were at random or not, we tested (chi-square) to evaluate if missing and nonmissing values (being parous, age at first live birth, age at last live birth, age at menarche, age at menopause, and menopausal status) were associated with risk factors for

bladder cancer in this study, i.e., age, cigarette smoking, and high-risk occupation among cases and controls respectively. We found missing values of age at first live birth were associated with smoking among cases; missing values of age at last live birth were associated with smoking among cases; missing values of age at menopause were associated with age and smoking among cases and with age among controls; missing values of menopausal status were associated with age and smoking among cases and with age among controls. Our overall findings were unlikely to have been affected by missing information. However, trends in risk with specific reproductive factors (e.g., age at first live birth, age at menarche) might have been affected.

In conclusion, we found that ever-parous Spanish women were at lower risk of bladder cancer than nulliparous women, suggesting a hormonal influence on risk. Further research on this subject is needed from other populations that may differ in their use of hormone replacement therapy and use of oral contraceptives. Women have a lower risk of bladder cancer than men, and hormonal factors related to being parous may play a role in the gender disparity.

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Table 1

Characteristics of the female population in the Spanish Bladder Cancer Study, 1998–2001

Variables	Bladder cancers (percentage of cancers)	Controls (percentage of controls)
No. of participants	152	166
Age		
<55	24 (16%)	20 (12%)
55–64	19 (13%)	23 (14%)
65–69	29 (19%)	34 (21%)
70–74	41 (27%)	40 (24%)
>74	39 (26%)	49 (30%)
Mean (±SD)	67.4 (±10)	67.8 (±9.5)
Marital status		
Single	18 (14%)	10 (7%)
Ever-married	114 (86%)	143 (94%)
Missing	20	13
High-risk occupation		
No	105 (90%)	121 (99%)
Yes	12 (10%)	1 (1%)
Missing	35	44
Cigarette smoking		
Never	109 (80%)	140 (92%)
Former	6 (4%)	6 (4%)
Current	21 (15%)	6 (4%)
Missing	16	14
Being parous		
Nulliparous	27 (21%)	15 (10%)
Ever-parous	102 (79%)	133 (90%)
Missing	23	18
Age at first birth		
<21	22 (22%)	19 (15%)
21–24	30 (29%)	53 (41%)
25–27	27 (27%)	30 (23%)
>27	23 (23%)	29 (22%)
Missing	50	35
Age at last birth		
<28	24 (24%)	27 (21%)
28–32	31 (30%)	42 (33%)
33–35	25 (25%)	16 (12%)
>35	22 (22%)	44 (34%)
Missing	50	37
Age at menarche		
<13	43 (36%)	51 (35%)

Variables	Bladder cancers (percentage of cancers)	Controls (percentage of controls)
13	23 (19%)	24 (17%)
14–15	29 (24%)	43 (30%)
>15	24 (20%)	26 (18%)
Missing	33	22
Age at menopause		
<47	34 (35%)	41 (36%)
47–51	41 (42%)	38 (33%)
≥52	23 (24%)	36 (31%)
Missing	54	51
Menopausal status		
Premenopausal	13 (9%)	10 (6%)
Postmenopausal	133 (92%)	151 (94%)
Missing	6	5

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for bladder cancer by nulli- and ever-parous status for all female subjects, never-smoked female subjects, and ever-smoked female subjects in the Spanish Bladder Cancer Study, 1998–2001

	All subjects				Never smoked cigarettes				Ever smoked cigarettes			
	Cases	**Controls**	**OR[a]**	**95% CI**	**Cases**	**Controls**	**OR[a]**	**95% CI**	**Cases**	**Controls**	**OR[a]**	**95% CI**
Nulliparous	27	15	1.0		20	12	1.0		7	3	1.0	
Ever-parous	102	133	0.43	0.2–0.9	89	125	0.39	0.2–0.8	13	8	0.62	0.1–3.2
Missing	23	18			16	17			7	1		
Total	152	166			125	154			27	12		

[a]Adjusted for age, smoking status, and high-risk occupation

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for bladder cancer by age at first live birth, age at last live birth among ever-parous female subjects and by at menarche, age at menopause, duration of menstruation (years), and menopausal status among all female subjects and ever-parous female subjects in the Spanish Bladder Cancer Study, 1998–2001

	All subjects					Ever-parous women				
	Cases	**Controls**	**OR[a]**	**95% CI**	***p* Trend**	**Cases**	**Controls**	**OR[a]**	**95% CI**	***p* Trend**
Age at first live birth										
<21						22	19	1.0		
21–24						30	53	0.50	0.2–1.1	
25–27						27	30	0.76	0.3–1.8	
>27						23	29	0.68	0.3–1.6	0.74
Missing						50	35			
Total						152	166			
Age at last live birth										
<28						24	27	1.0		
28–32						31	42	0.72	0.3–1.5	
33–35						25	16	1.63	0.7–3.9	
>35						22	44	0.59	0.3–1.3	0.42
Missing						50	37			
Total						152	166			
Age at menarche										
<13	43	51	1.0			32	44	1.0		
13	23	24	0.97	0.5–2.0		20	21	1.14	0.5–2.5	
14–15	29	43	0.80	0.4–1.5		23	42	0.75	0.4–1.5	
>15	24	26	1.17	0.6–2.4	0.75	21	22	1.39	0.6–3.0	0.59
Missing	33	22				6	4			
Total	152	166				102	133			
Age at menopause										
<47	34	41	0.70	0.4–1.4		26	36	0.65	0.3–1.3	
47–51	41	38	1.0			33	34	1.0		
≥52	23	36	0.58	0.3–1.2		20	33	0.59	0.3–1.3	

	All subjects					Ever-parous women				
	Cases	**Controls**	**OR[a]**	**95% CI**	***p* Trend**	**Cases**	**Controls**	**OR[a]**	**95% CI**	***p* Trend**
Missing	54	51				23	30			
Total	152	166				102	133			
Duration of menstruation (years)										
≥39	25	35	1.0			20	31	1.0		
35–38.9	32	35	1.35	0.7–2.8		27	32	1.44	0.7–3.1	
31–34.9	22	20	1.60	0.7–3.6		16	19	1.41	0.6–3.4	
<31	28	33	1.11	0.5–2.3	0.79	23	28	1.20	0.5–2.7	0.75
Missing	45	43				16	23			
Total	152	166				102	133			
Menopausal status										
Premenopausal	13	10	1.0			10	9	1.0		
Postmenopausal	133	151	0.53	0.2–1.8		90	121	0.58	0.1–2.3	
Missing	6	5				2	3			
Total	152	166				102	133			

[a] Adjusted for age, smoking status, and high-risk occupation