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Research Article

Lower Risk in Parous Women Suggests That Hormonal Factors Are Important in Bladder Cancer Etiology

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Abstract

Background: Urinary bladder cancer is two to four times more common among men than among women, a difference in risk not fully explained by established risk factors. Our objective was to determine whether hormonal and reproductive factors are involved in female bladder cancer.

Methods: We analyzed data from two population-based studies: the Los Angeles–Shanghai Bladder Cancer Study, with 349 female case–control pairs enrolled in Los Angeles and 131 female cases and 138 frequency-matched controls enrolled in Shanghai, and the California Teachers Study (CTS), a cohort of 120,857 women with 196 incident cases of bladder urothelial carcinoma diagnosed between 1995 and 2005. We also conducted a meta-analysis summarizing associations from our primary analyses together with published results.

Results: In primary data analyses, parous women experienced at least 30% reduced risk of developing bladder cancer compared with nulliparous women (Shanghai: OR = 0.38, 95% CI: 0.13–1.10; CTS: RR = 0.69, 95% CI: 0.50–0.95) consistent with results of a meta-analysis of nine studies (summary RR = 0.73, 95% CI: 0.63–0.85). The CTS, which queried formulation of menopausal hormone therapy (HT), revealed a protective effect for use of combined estrogen and progestin compared with no HT (RR = 0.60, 95% CI: 0.37–0.98). Meta-analysis of three studies provided a similar effect estimate (summary RR = 0.65, 95% CI: 0.48–0.88).

Conclusions: A consistent pattern of reduced bladder cancer risk was found among parous women and those who used estrogen and progestin for HT.

Impact: These results suggest that more research is warranted to investigate hormonal and reproductive factors as possible contributors to bladder cancer risk. *Cancer Epidemiol Biomarkers Prev; 20(6); 1156–70. ©2011 AACR.*

Introduction

Urinary bladder cancer is the fifth most common malignancy in industrialized nations. In the United States, 70,530 incident cases and 14,680 bladder cancer deaths were anticipated in 2010 (1), of which more than 90% are urothelial carcinoma (UC). Cigarette smoking and occupational exposure to several arylamine compounds are established UC risk factors (2).

Occupational exposure to carcinogenic arylamines was dramatically reduced in the United States by banning use of 2-napthylamine, ceasing large-scale use of benzidine, and substituting other compounds for 4-aminobiphenyl (3). Approximately half of UC diagnoses are now attributed to cigarette smoke (4), which contains 4-aminobiphenyl and 2-napthylamine (3), but etiology among nonsmokers remains largely unknown.

Incidence is notably greater among men; age-adjusted U.S. rates (U.S. standard population, 2000) were 37.2/100,000 for men and 9.2/100,000 for women during 2003–2007 (1). Established risk factors do not explain this disparity: absent exposure to cigarettes, occupational hazards, and urinary tract infections, men experience an estimated 2.7 times the risk of women (5). Postulated explanations include gender differences in lifestyle (2), anatomy (5), and hormones (6).

Mechanisms involving steroid hormones seem plausible because there are fundamental gender differences in production and response to these compounds, and the androgen receptor (AR), estrogen receptors (ER), and

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progesterone receptors (PR) are expressed in the human bladder (7–12). In rodent models, estrogens inhibit and androgens promote bladder tumor growth (13, 14), incidence of chemically induced bladder tumors is significantly greater among male animals (15), and parous females have significantly smaller bladder tumors than nulliparous females (16).

Hormonal and reproductive factors have not been a major focus of human bladder cancer research, possibly due to small numbers of women enrolled in studies (17–29). Two studies reported reduced risk among parous women (21, 27); additional studies addressing parity are consistent with this effect, although not statistically significant (17–19, 26, 29). To further investigate associations between hormonal and reproductive factors and UC risk among women, we analyzed data from 2 large studies—the Los Angeles–Shanghai Bladder Cancer Study and the California Teachers Study (CTS), placing results in context with published reports.

Materials and Methods

The Los Angeles–Shanghai Bladder Cancer Study

Study population. This population-based case–control study was conducted at sites representing high [Los Angeles County (LA), California] and low (city of Shanghai, China) UC risk, as described (4, 30). In LA, the Los Angeles County Cancer Surveillance Program (31), a National Cancer Institute Surveillance, Epidemiology and End Results (SEER) registry, identified incident UC cases diagnosed between 1987 and 1996 among non-Asians aged 25 to 64 years. Of 2,384 eligible cases, 210 died before being contacted or were too ill to participate, physicians denied permission to contact 99 cases, 404 declined participation, and 1,671 (71%) were interviewed. Controls were identified by standard procedure within cases' neighborhood of residence (4), and individually matched to cases on sex, age (within 5 years), race/ethnicity (non-Hispanic white, Hispanic white, African American), and neighborhood. The first neighborhood resident identified satisfying all control eligibility requirements was asked to participate (i.e., first eligible control). If that individual refused, the next eligible control (i.e., second eligible control) in sequence was recruited, and so on, until an eligible control was located. Among 1,586 enrolled controls, 1,090 (69%) were first eligible controls, 325 (20%) were second eligible controls, 111 (7%) were third eligible controls, and the remaining 60 (4%) were fourth or higher eligible controls.

In Shanghai, the Shanghai Cancer Registry identified Han Chinese residents of Shanghai aged 25 to 74 years when diagnosed with bladder cancer between 1995 and 1998. Of 749 cases identified, 56 died before being contacted or were too ill to participate, 29 declined participation, 42 were not located, and 622 (83%) were interviewed. Population-based controls were Han Chinese, selected from Shanghai residents by an established algorithm (32), and frequency-matched to cases by 5-year age groups. Among 726 randomly selected controls, 72 declined participation, 44 were not located, and 610 (84%) were interviewed. All participants signed consent forms. This analysis is limited to women: 349 case–control pairs from LA, and 131 cases and 138 controls from Shanghai.

Data collection. Participants were interviewed at home by trained interviewers using structured questionnaires standardized across study sites. To establish a reference year, cases were asked to provide information up to 2 years before cancer diagnosis and controls up to 2 years before the matched case's diagnosis (LA) or 2 years before interview (Shanghai). Questionnaires covered demographic characteristics, diet, alcohol intake, tobacco use, medical history, and hormonal and reproductive history. Use of hair dyes and nonsteroidal anti-inflammatory drugs (NSAID) were collected only in LA.

In LA, women were asked about the total number of pregnancies and whether they had undergone hysterectomy. In Shanghai, women were asked about the number of sons and daughters to whom they had given birth. Standard reproductive factors not collected at either site are as follows: age at menarche, age at first birth, breast-feeding history, menopausal status, age at menopause, and history of oophorectomy.

At both sites, women were asked about the use of hormones for contraception. In LA, women were asked about estrogen use for menopausal hormone therapy (HT). In Shanghai, women were asked about the use of estrogen injections for menopausal symptoms. Progestin use was not queried at either site. History of cigarette smoking, cigarette smoking status, and number of cigarettes smoked per day were collected. Smoking status was categorized as never, former, or current. Ever smokers reported smoking 100 or more cigarettes during their lives. Pack-years of smoking were calculated for ever smokers. Body mass index (BMI) was calculated and categorized using WHO guidelines (33).

Statistical analysis. Associations were measured by ORs and corresponding 95% CIs. Most analyses of LA data used matched-pairs conditional logistic regression, although analyses stratified on smoking history [never smokers vs. ever (current or former) smokers] used unconditional logistic regression. Shanghai data were analyzed using unconditional logistic regression with adjustment for age. All models were adjusted for smoking status in the reference year (current, former, never), pack-years of smoking, and BMI (16–19.9, 20–24.9, 25–29.9, $\geq$30, values <16 or $\geq$55 were coded unknown). Pack-years of smoking were included in analyses among ever smokers. Estimates of main effects did not change by 10% or more with further adjustment of Shanghai data for parity or education, or LA data for NSAID use, carotenoid intake, hair dye use, education, or pregnancy history, so these variables were not retained. Analyses were performed using SAS version 9.1 (SAS Institute). Wald tests for trend were conducted with exposures coded as ordinal variables. Reported P values are 2-sided.

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The California teachers study

Study population. A detailed description of the CTS cohort is published (34). The cohort is composed of current, former, and retired female public school professionals who were members of the California State Teachers Retirement System in 1995 when the study began. Cohort members completed a detailed, mailed questionnaire that queried information on many factors including menstrual and reproductive history, medical history, menopausal HT, diet, physical activity, alcohol intake, and smoking. All collaborating institutions received Institutional Review Board approval for the study. The cohort is composed of 133,479 women. For this analysis, sequential exclusion for history of bladder cancer ($n = 130$), unknown history of cancer ($n = 662$), residing outside California at baseline ($n = 8{,}867$), consenting to participate only in breast cancer research ($n = 18$), baseline age 85 or older ($n = 2{,}199$), unacceptable questionnaire ($n = 2$), and unknown smoking history ($n = 731$) yielded a potential analytic cohort of 120,870.

Case ascertainment and follow-up. Incident cases of invasive bladder cancer (International Classification of Diseases for Oncology ICD-O-2 site codes C67.0–C67.9) were identified through linkage to the California Cancer Registry, which receives information on diagnoses in California on the basis of state mandate established in 1985, estimated to be 99% complete (35). During follow-up (1995–2005), 209 incident, invasive bladder tumors (including *in situ*) were diagnosed among the analytic cohort. After excluding 13 diagnosed with non-UC bladder tumors, 120,857 women remained in this analysis, including 196 UC cases (ICD-O-2 histology codes 8120 and 8130).

Person-time accrued from date of completion of baseline questionnaire until date of first diagnosis with UC or first censoring event [relocation out of California for more than 4 months; death; end of follow-up (December 31, 2005); or $\geq$85 years of age]. Residence in California was determined through annual mailings of newsletters, linkage with U.S. Postal Service National Change of Address database, and change-of-address postcards submitted by participants. Date and cause of death were obtained through California state mortality files, the Social Security Administration death master file, and the National Death Index.

Exposure assessment. Exposure measures are based on participants' responses to the baseline questionnaire. Pregnancy history included all pregnancies, whereas parity was restricted to full-term pregnancies (live births and stillbirths).

Menopausal status was determined using answers to detailed questions about history of menstrual periods, hysterectomy, and ovarian surgeries with categories (premenopausal, perimenopausal, postmenopausal, unknown menopausal status) defined as described (36).

HT use was categorized by duration, formulation [estrogen alone, estrogen–progestin combination (E + P)], and as never, past, or current use as described (36).

Age at menarche, use of oral contraceptives (OC), and breast-feeding history were categorized as described (36).

The baseline questionnaire collected race/ethnicity. BMI was calculated and categorized (33). History of cigarette smoking, cigarette smoking status, and number of cigarettes smoked per day were collected. Smoking status was categorized as never, former, or current. Ever smokers reported smoking 100 or more cigarettes during their lives. Pack-years of smoking were calculated for ever smokers.

Identical definitions were used for all variables shared across the CTS and case–control studies except for 3: age, for which age at reference year was used in the case–control study and age at baseline was used in the CTS, and 2 variables defined in detail earlier (pregnancy in LA vs. full-term pregnancy in the CTS, and categories of HT formulation queried in LA vs. the CTS).

Statistical analysis. Multivariate Cox proportional hazards regression was used to estimate associations. Hazard rate ratios, presented as relative risks (RR) with 95% CIs, were estimated using age in days at baseline as the time metric, stratified on age at baseline (in single years). Models estimating associations with UC risk were adjusted for race/ethnicity (non-Hispanic white, African American, Hispanic white, Asian/Pacific Islander, other/mixed race, unknown), smoking status (never, former, current), and BMI (16–19.9, 20–24.9, 25–29.9, $\geq$30 kg/m^2, values <16 or $\geq$55 were coded unknown). We adjusted for smoking status as the only measure of smoking history, as additional inclusion of pack-years did not alter inference. Other potential confounders included alcohol intake, use of NSAIDs, history of diabetes and physical activity, parity, and HT use. These were not included in the final model because, with a single exception (noted in text), adjustment did not change estimates of main effects by 10% or more. Wald tests for trend were conducted with exposures coded as ordinal variables. Missing values were included as indicator variables, and in all instances were not found to be associated with UC risk. Tests of significance were 2-sided. The proportional hazards assumption was assessed for each key hormonal and reproductive variable by examining Kaplan–Meier curves and plotting scaled Schoenfeld residuals to test for zero slope. No evidence of violation of the proportional hazards assumption was detected.

Analyses were conducted on eligible women with the following exclusions: 31,511 women with no full-term pregnancy were excluded from analyses of pregnancy and breast-feeding; 47,750 premenopausal and 2,476 perimenopausal women were excluded from analyses of age at menopause; and 47,750 premenopausal women were excluded from analyses of HT. Associations between hormonal and reproductive exposures and UC were stratified on smoking history [never smokers vs. ever (current or former) smokers], with pack-years of smoking included as a covariate in analyses among ever smokers.

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Analyses were conducted using SAS statistical software (version 9.1; SAS Institute).

Meta-analysis

We searched MEDLINE and PubMed for articles published in English through December 2010, selecting publications that (i) included a case group of women diagnosed with bladder cancer, (ii) analyzed associations between hormonal and/or reproductive exposures and bladder cancer risk, and (iii) addressed effects of smoking. Twelve articles met these criteria (17–25, 27–29). Two provided data on the same cohort (18, 20); we retained the more recently published article (18).

We analyzed effects of ever versus never exposure to parity, use of OCs, use of any HT, use of E + P for HT, and use of estrogen alone for HT. One study (18) did not provide risk estimates for ever versus never parous but did compare nulliparous women to each of several parous categories defined by number of births. To include data from this study, we first calculated RRs and variance estimates for ever versus never parous by weighing reported RRs and variance estimates for each parous category by the corresponding number of person-years.

Analyses were conducted using Stata statistical software (Stata/SE 9.0; StataCorp). For each analysis, we estimated summary RRs and corresponding 95% CIs and graphically displayed estimates from each study and the summary estimate in a Forrest plot.

Variation due to differences in design and conduct of studies may manifest as between-study heterogeneity, which we assessed in each analysis by calculating between-study heterogeneity P values (38) and I^2 (percentage of variation in summary estimate due to heterogeneity between studies) statistics (37) and creating Begg's funnel plots (39). I^2 range is 0% to 100%, higher values indicating greater heterogeneity (0%–30%, mild; 30%–50%, moderate; 50%–100%, notable; ref. 37). Begg's funnel plots display the RR estimate versus standard error of the RR for each study; in the absence of between-study heterogeneity, sampling variation alone tends to distribute results within the "funnel" defined by pseudo 95% confidence limits. In the single analysis in which some studies were outside these limits, we repeated the meta-analysis excluding outlying studies and report results for full and restricted sets of studies.

For a single analysis stratified on smoking history, we assessed heterogeneity of effects between ever smokers and never smokers by estimating a between-strata heterogeneity P value. Publication bias was assessed in all analyses on the basis of the P value from Begg's test (39).

Results

The Los Angeles–Shanghai Bladder Cancer Study

Characteristics of cases and controls appear in Supplemental Table S1. Estimates of risk factor associations are given in Table 1; only never smokers from Shanghai are presented, as there were few ever smokers from this site ($n = 26$), and results for Shanghai never smokers are similar to those for all Shanghai participants.

Among all women in LA, risk was lower among those who were ever pregnant (OR = 0.58, 95% CI: 0.33–0.98). Similarly, among all women in Shanghai, risk was lower among those who were parous (OR = 0.38, 95% CI: 0.13–1.10; not shown in Table 1). However, there was no apparent trend over number of births (or pregnancies) or age at first birth (or pregnancy; Table 1). In analyses stratified on smoking history, effects of pregnancy were greater among never smokers in LA (never smokers: OR = 0.30, 95% CI: 0.13–0.65; ever smokers: OR = 1.29, 95% CI: 0.71–2.35), as were effects of parity in Shanghai (never smokers: OR = 0.35, 95% CI: 0.11–1.08; ever smokers: OR = 0.87, 95% CI: 0.05–15.0; not shown in Table 1).

Bladder cancer risk was not statistically significantly associated with ever using OCs (LA: OR = 0.81, 95% CI: 0.55–1.19; Shanghai never smokers: OR = 0.82, 95% CI: 0.38–1.79).

In LA, use of estrogen for HT was not associated with bladder cancer risk (OR = 0.96, 95% CI: 0.65–1.42). However, data were not collected on use of progestin for HT and data from Shanghai were too sparse to estimate effects of using estrogen for HT.

Among additional reproductive factors, hysterectomy, assessed only in LA, was not significantly associated with risk (OR = 1.16, 95% CI: 0.79–1.69). Among Shanghai participants, there was a distinct association of risk with increasing BMI ($P_{trend} = 0.008$) among never smokers. However, no such pattern was observed among LA participants. Among never smokers in LA, no factor other than pregnancy history was associated with risk.

The California Teachers Study

Characteristics of cohort members are given in Supplemental Table S2. Estimates of risk factor associations are given in Table 2. Ever pregnant and parous women had significantly lower UC risk than never pregnant or nulliparous women (ever pregnant: RR = 0.60, 95% CI: 0.43–0.83; parous: RR = 0.69, 95% CI: 0.50–0.95; Table 2). Among parous women, risk was not associated with age at first full-term pregnancy, number of full-term pregnancies, or history of breast-feeding. Among all women, neither age at menarche nor history of OC use was associated with risk.

Postmenopausal women did not have increased UC risk compared with pre- and perimenopausal women (RR = 1.02, 95% CI: 0.48–2.19 for natural menopause; RR = 1.39, 95% CI: 0.63–3.09 for menopause due to bilateral oophorectomy). No significant association was found for age at menopause, hysterectomy, oophorectomy, or BMI.

Among perimenopausal and postmenopausal women, use of estrogen alone for HT was not associated with risk (RR = 1.18, 95% CI: 0.83–1.70). Women who used E + P for HT experienced significantly lower risk than those who used no HT (RR = 0.60, 95% CI: 0.37–0.98). No case reported using only progestin.

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Table 1. Adjusted ORs and 95% CIs for associations between hormonal and reproductive factors and risk of bladder cancer among women in the Los Angeles–Shanghai Bladder Cancer Study

	Los Angeles				Shanghai	
	Cases/controls (all women)	All women OR (95% CI)[a]	Never smokers OR (95% CI)[b]	Ever smokers OR (95% CI)[b]	Cases/controls (nonsmokers)	Never smokers OR (95% CI)[c]
Parity						
Nulliparous	–	–	–	–	11/5	1.0 (ref)
Parous	–	–	–	–	102/125	0.35 (0.11–1.08)
Number of children						
1	–	–	–	–	27/22	1.0 (ref)
2	–	–	–	–	25/25	0.63 (0.23–1.74)
3	–	–	–	–	17/28	0.47 (0.16–1.33)
≥4	–	–	–	–	33/50	0.56 (0.21–1.48)
						$P_{trend} = 0.31$
Pregnancy						
Never	45/37	1.0 (ref)	1.0 (ref)	1.0 (ref)	–	–
Ever	304/312	**0.58 (0.33–0.98)**	**0.30 (0.13–0.65)**	1.29 (0.71–2.35)	–	–
Total number of pregnancies						
1	44/32	1.0 (ref)	1.0 (ref)	1.0 (ref)	–	–
2	64/85	0.41 (0.19–0.87)	0.42 (0.14–1.22)	0.71 (0.35–1.44)	–	–
3	69/72	0.63 (0.29–1.34)	0.42 (0.12–1.37)	0.75 (0.37–1.51)	–	–
≥4	127/123	0.70 (0.35–1.39)	0.79 (0.29–2.18)	0.84 (0.43–1.62)	–	–
		$P_{trend} = 0.73$	$P_{trend} = 0.82$	$P_{trend} = 0.93$		
OC use						
Never	170/170	1.0 (ref)	1.0 (ref)	1.0 (ref)	95/110	1.0 (ref)
Ever	177/179	0.81 (0.55–1.19)	1.40 (0.75–2.62)	0.83 (0.55–1.24)	18/20	0.82 (0.38–1.79)
Duration of OC use						
Nonuser	170/170	1.0 (ref)	1.0 (ref)	1.0 (ref)	95/110	1.0 (ref)
<4 y	84/86	0.74 (0.47–1.18)	1.54 (0.70–3.36)	0.76 (0.48–1.22)	12/11	0.92 (0.36–2.37)
≥4 y	88/93	0.79 (0.50–1.25)	1.11 (0.53–2.32)	0.88 (0.54–1.43)	6/9	0.68 (0.22–2.16)
		$P_{trend} = 0.28$	$P_{trend} = 0.51$	$P_{trend} = 0.54$		$P_{trend} = 0.54$

(Continued on the following page)

Table 1. Adjusted ORs and 95 CIs for associations between hormonal and reproductive factors and risk of bladder cancer among women in the Los Angeles–Shanghai Bladder Cancer Study (Cont'd)

	Los Angeles				Shanghai	
	Cases/controls (all women)	All women OR (95% CI)[a]	Never smokers OR (95% CI)[b]	Ever smokers OR (95% CI)[b]	Cases/controls (nonsmokers)	Never smokers OR (95% CI)[c]
Menopausal estrogen therapy use						
Never	193/194	1.0 (ref)	1.0 (ref)	1.0 (ref)	–	–
Ever	156/154	0.96 (0.65–1.42)	1.00 (0.54–1.86)	1.03 (0.70–1.54)	–	–
Duration of estrogen use						
Nonuser	193/194	1.0 (ref)	1.0 (ref)	1.0 (ref)	–	–
<4 y	76/70	1.11 (0.69–1.80)	1.02 (0.48–2.17)	1.13 (0.69–1.86)	–	–
≥4 y	80/84	0.86 (0.54–1.38)	1.00 (0.47–2.14)	0.96 (0.60–1.54)	–	–
		$P_{trend} = 0.61$	$P_{trend} = 0.98$	$P_{trend} = 0.93$		
Hysterectomy						
Never	233/243	1.0 (ref)	1.0 (ref)	1.0 (ref)	–	–
Ever	116/106	1.16 (0.79–1.69)	0.83 (0.44–1.58)	1.23 (0.82–1.86)	–	–
BMI						
16–19.9	70/39	2.25 (1.29–3.92)	1.90 (0.78–4.64)	1.84 (1.08–3.11)	13/23	0.67 (0.31–1.47)
20–24.9	194/207	1.0 (ref)	1.0 (ref)	1.0 (ref)	67/87	1.0 (ref)
25–29.9	54/66	0.72 (0.44–1.22)	0.79 (0.36–1.75)	0.82 (0.49–1.37)	30/18	2.31 (1.14–4.47)
≥30	30/36	1.46 (0.77–2.78)	0.55 (0.23–1.33)	2.73 (1.06–7.03)	3/2	2.11 (0.33–13)
		$P_{trend} = 0.12$	$P_{trend} = 0.10$	$P_{trend} = 0.52$		$P_{trend} = 0.008$

[a]Conditional logistic regression adjusted for age at reference year, race/ethnicity (non-Hispanic white, Hispanic white, or African American), smoking status (never, former, or current), pack-years of smoking, and BMI (<20, 20–24.9, 25–29.9, ≥30, unknown).

[b]Unconditional logistic regression adjusted for age at reference year, race/ethnicity (non-Hispanic white, Hispanic white, or African American), and BMI (<20, 20–24.9, 25–29.9, ≥30, unknown).

[c]Unconditional logistic regression adjusted for age at reference year and BMI (<20, 20–24.9, 25–29.9, ≥30, unknown).

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Table 2. Adjusted relative risks and 95% confidence intervals for associations between selected menstrual, hormonal and reproductive factors and risk of bladder cancer in the CTS

Characteristics	All women			Never smokers			Ever smokers		
	Total (N = 120,857)	Cases (n = 196	RR (95% CI)[a]	Total (N = 79,886)	Cases (n = 82)	RR (95% CI)[b]	Total (N = 40,971)	Cases (n = 115)	RR (95% CI)[b]
Pregnancy									
Never	24,459	48	1.0 (ref)	17,026	22	1.0 (ref)	7,433	26	1.0 (ref)
Ever	94,944	141	**0.60 (0.43–0.83)**	61,927	58	**0.53 (0.32–0.87)**	33,017	83	0.65 (0.42–1.01)
Unknown or missing	1,454	7		933	2		521	5	
Parity[c]									
Nulliparous	31,511	52	1.0 (ref)	21,179	23	1.0 (ref)	10,332	29	1.0 (ref)
Parous	87,735	137	**0.69 (0.50–0.95)**	57,636	57	0.61 (0.37–1.00)	30,099	80	0.76 (0.49–1.16)
Unknown or missing	1,611	7		1,071	2		540	5	
Age at first full-term pregnancy[d]									
<20	4,491	5	0.78 (0.31–1.95)	2,715	4	1.77 (0.61–5.21)	1,776	1	0.24 (0.03–1.78)
20–25	34,828	62	1.0 (ref)	22,098	21	1.0 (ref)	12,730	41	1.0 (ref)
26–30	32,603	51	1.10 (0.76–1.62)	22,213	22	1.22 (0.66–2.25)	10,390	29	1.04 (0.64–1.68)
>30	14,992	19	1.00 (0.59–1.71)	10,030	10	1.30 (0.58–2.82)	4,962	9	0.86 (0.41–1.80)
Unknown or missing	2,432	7		1,651	2		781	5	
			P_{trend} = 0.56			P_{trend} = 0.92			P_{trend} = 0.49
Total number of full-term pregnancies[d]									
1	18,610	24	1.0 (ref)	12,141	11	1.0 (ref)	6,469	13	1.0 (ref)
2	38,878	60	1.14 (0.71–1.86)	25,808	25	0.98 (0.49–2.00)	13,070	35	1.28 (0.68–2.43)
3	19,235	27	0.73 (0.42–1.27)	12,491	9	0.52 (0.22–1.26)	6,744	18	0.91 (0.44–1.89)
4+	10,193	26	1.06 (0.61–1.87)	6,617	12	1.04 (0.46–2.56)	3,576	14	1.06 (0.49–2.30)
Unknown or missing	2,430	7		1,650	2		780	5	
			P_{trend} = 0.60			P_{trend} = 0.68			P_{trend} = 0.73
Breast-feeding[d]									
Never breast-fed	19,684	46	1.0 (ref)	11,622	19	1.0 (ref)	8,062	27	1.0 (ref)
Ever breast-fed	67,003	91	0.93 (0.64–1.33)	45,311	38	0.79 (0.45–1.37)	21,692	53	1.05 (0.66–1.67)
Unknown or missing	2,659	7		1,774	2		885	5	
Age at menarche									
<12	26,959	41	1.0 (ref)	17,878	22	1.0 (ref)	9,081	19	1.0 (ref)
12	32,606	55	1.08 (0.72–1.62)	21,503	19	0.68 (0.37–1.27)	11,103	36	1.51 (0.87–2.64)
13	35,116	52	0.91 (0.60–1.38)	23,263	21	0.67 (0.37–1.22)	11,853	31	1.16 (0.65–2.06)
14+	24,432	41	0.94 (0.61–1.46)	16,107	17	0.71 (0.37–1.35)	8,325	24	1.18 (0.64–2.16)
Unknown or missing	1,744	7		1,135	3		609	4	
			P_{trend} = 0.62			P_{trend} = 0.42			P_{trend} = 0.98

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Table 2. Adjusted relative risks and 95 confidence intervals for associations between selected menstrual, hormonal and reproductive factors and risk of bladder cancer in the CTS (Cont'd)

Characteristics	All women			Never smokers			Ever smokers		
	Total ($N = 120,857$)	Cases ($n = 196$	RR (95% CI)[a]	Total ($N = 79,886$)	Cases ($n = 82$)	RR (95% CI)[b]	Total ($N = 40,971$)	Cases ($n = 115$)	RR (95% CI)[b]
OC use									
Never user	38,408	107	1.0 (ref)	25,463	48	1.0 (ref)	12,945	59	1.0 (ref)
Ever user	78,890	79	1.05 (0.73–1.50)	52,018	29	0.92 (0.51–1.67)	26,872	50	1.09 (0.70–1.69)
Unknown or missing	3,559	10		2,405	5		1,154	5	
Menopausal status									
Pre- or perimenopausal	50,226	15	1.0 (ref)	37,989	10	1.0 (ref)	12,237	5	1.0 (ref)
Postmenopausal, natural	35,045	100	1.02 (0.48–2.19)	20,202	35	0.71 (0.25–2.04)	14,843	65	1.49 (0.46–4.82)
Postmenopausal, surgical[e]	10,172	30	1.39 (0.63–3.09)	6,200	14	1.25 (0.42–3.69)	3,972	16	1.70 (0.50–5.80)
Unknown[e] or missing	25,414	51		15,495	23		9,919	28	
Age at menopause[f]									
≥53	11,097	35	1.0 (ref)	6,614	11	1.0 (ref)	4,483	24	1.0 (ref)
47–52	21,776	64	1.02 (0.68–1.55)	12,580	26	1.41 (0.69–2.86)	9,196	38	0.85 (0.50–1.42)
44–46	5,889	15	0.94 (0.51–1.73)	3,409	7	1.44 (0.56–3.76)	2,480	8	0.71 (0.32–1.58)
≤43	6,455	16	1.07 (0.59–1.93)	3,799	5	1.11 (0.38–3.23)	2,656	11	1.02 (0.50–2.10)
Unknown[g] or missing	25,414	51		15,495	23		9,919	28	
			$P_{trend} = 0.93$			$P_{trend} = 0.72$			$P_{trend} = 0.83$
Hysterectomy									
Never	90,149	106	1.0 (ref)	60,875	40	1.0 (ref)	29,274	66	1.0 (ref)
Ever	28,154	81	1.29 (0.97–1.74)	17,305	39	1.61 (1.02–2.55)	10,849	42	1.09 (0.74–1.62)
Unknown or missing	2,554	9		1,706	3		848	6	
Ovary removed									
None	98,985	138	1.0 (ref)	66,549	56	1.0 (ref)	32,436	82	1.0 (ref)
One removed	5,610	14	1.13 (0.66–1.97)	3,360	5	1.10 (0.74–2.76)	2,250	9	1.17 (0.58–2.33)
Both removed	14,470	40	1.14 (0.81–1.63)	8,840	18	1.26 (0.74–2.16)	5,630	22	1.07 (0.66–1.71)
Unknown or missing	1,792	4		1,137	3		655	1	
BMI									
16–19.9	12,608	14	0.80 (0.46–1.42)	8,938	6	0.83 (0.35–1.98)	3,670	8	0.82 (0.39–1.73)
20–24.9	58,085	94	1.0 (ref)	38,526	38	1.0 (ref)	19,559	56	1.0 (ref)
25–29.9	29,009	44	0.77 (0.54–1.10)	18,689	19	0.84 (0.48–1.45)	10,320	25	0.73 (0.45–1.16)
≥30	16,370	26	0.97 (0.64–1.50)	10,724	12	1.09 (0.58–2.11)	5,646	14	0.85 (0.47–1.53)
Unknown or missing	4,785	18		3,009	7		1,776	11	
			$P_{trend} = 0.85$			$P_{trend} = 0.82$			$P_{trend} = 0.49$
Ever use of menopausal HT[h]									
Never HT user	16,713	49	1.0 (ref)	10,379	24	1.0 (ref)	6,334	25	1.0 (ref)

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Ever HT user	50,928	120	0.93 (0.66–1.31)	29,781	45	0.78 (0.47–1.28)	21,147	75	1.01 (0.64–1.60)
Unknown or missing	5,466	16		3,301	6		5,165	10	
Type of HT used[h]									
Never HT user	16,713	49	1.0 (ref)	10,379	24	1.0 (ref)	6,334	25	1.0 (ref)
Estrogen alone only user	20,956	75	1.18 (0.83–1.70)	12,668	30	0.98 (0.57–1.68)	8,288	45	1.31 (0.80–2.14)
E + P only user	20,524	26	**0.60 (0.37–0.98)**	11,669	9	0.49 (0.22–1.10)	8,855	17	0.65 (0.35–1.24)
E alone and E + P user	7,010	16	0.75 (0.42–1.32)	3,914	6	0.70 (0.28–1.73)	3,096	10	0.76 (0.36–1.58)
P alone and E + P user	2,177	3	0.74 (0.23–2.41)	1,363	0	–	814	3	1.41 (0.42–4.72)
Unknown or missing	5,727	16		3,468	6		2,259	10	
Past or current estrogen and progestin use[h]									
Never HT user	16,713	49	1.0 (ref)	10,379	24	1.0 (ref)	6,334	25	1.0 (ref)
Past E + P user	3,063	7	0.93 (0.42–2.06)	1,696	3	0.98 (0.29–3.33)	1,367	4	0.87 (0.30–2.51)
Current E + P user	17,046	19	**0.55 (0.31–0.95)**	9,740	6	0.40 (0.15–1.02)	7,306	13	0.62 (0.31–1.25)
E alone user	20,956	75	1.18 (0.83–1.70)	12,668	30	0.98 (0.57–1.67)	8.288	45	1.31 (0.80–2.14)
E alone and E + P or P alone and E + P user	9,863	19	0.72 (0.42–1.22)	5,677	6	0.55 (0.22–1.35)	4,186	13	0.82 (0.42–1.60)
Unknown or missing	5,466	16		3,301	6		2,165	10	
Duration of estrogen and progestin use[h]									
Never HT user	16,713	49	1.0 (ref)	10,379	24	1.0 (ref)	6,334	25	1.0 (ref)
E + P only user, <1–2 y	7,196	9	0.73 (0.35–1.54)	4,312	4	0.70 (0.23–2.11)	2,884	5	0.72 (0.27–1.93)
E + P only user, 3+ y	12,448	17	0.61 (0.35–1.08) $P_{trend} = 0.11$	6,865	5	0.45 (0.17–1.22) $P_{trend} = 0.13$	5,583	12	0.69 (0.34–1.40) $P_{trend} = 0.35$
E alone, or E alone and E + P or P alone and E + P user	31,284	94	1.04 (0.73–1.47)	18,604	36	0.86 (0.52–1.44)	12,680	58	1.14 (0.71–1.82)
Unknown or missing	5,466	16		3,301	6		2,165	10	

[a]Stratified on age at baseline and adjusted for smoking status (never, former, current), race/ethnicity (non-Hispanic white, African American, Hispanic white, Asian/Pacific Islander, mixed or other race, unknown), and BMI (<25, 25–29.9, 30+, unknown).

[b]Stratified on age at baseline and adjusted for race/ethnicity (non-Hispanic white, African American, Hispanic white, Asian/Pacific Islander, mixed or other race, unknown) and BMI (<25, 25–29.9, 30+, unknown).

[c]Nulliparous includes women who were never pregnant or did not have a full-term pregnancy.

[d]Excluding women with no full-term pregnancies.

[e]Surgical menopause was defined as undergoing a bilateral oophorectomy before occurrence of natural menopause.

[f]Pre- and perimenopausal women excluded.

[g]Includes women who underwent a hysterectomy before age 56 and were younger than 56 years at baseline, or had menopause due to chemotherapy or radiation, or had menopause due to other reasons, or had unknown menopausal status due to HT.

[h]Premenopausal women excluded.

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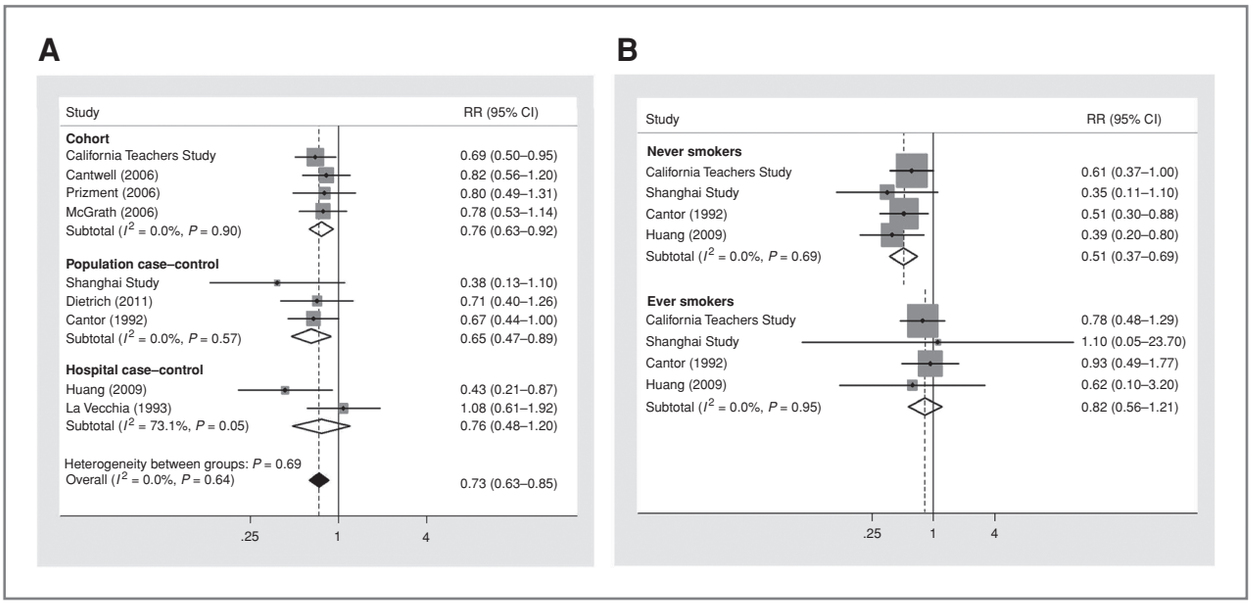

Figure 1. Forrest plots displaying contributing data and results of meta-analyses relating parity to risk of bladder cancer: among all women (A); within strata of smoking history (B). Summary RR (SRR), top and bottom points of diamond; 95% CI of SRR, left and right points of diamond; stratum-specific SRR, open diamond; overall SRR, filled diamond. Individual study RR estimate and 95% CI, point and horizontal line; relative weight, box size.

Among never smokers, parity (RR = 0.61, 95% CI: 0.37–1.00) and use of E + P for HT appeared protective (RR = 0.49, 95% CI: 0.22–1.10), although associations were not statistically significant. The association with history of hysterectomy was not significant when HT use (never, ever estrogen alone, ever other formulation) was included in the model (RR = 1.65, 95% CI: 0.96–2.81).

Estimates of pregnancy–UC associations were similar to estimates of parity–UC associations in all analyses.

Meta-analysis

Reports included in the meta-analysis are enumerated in Supplemental Table S3. Seven provided data on parity, of which 2 also provided parity data stratified by smoking history; 5 provided data on OC use; 8 provided data on any use of HT, of which 2 specified HT formulation. Associations between these factors and bladder cancer, estimated for individual studies and in summary estimates, are displayed in Forrest plots (Figs. 1 and 2), with summary estimates provided for subgroups of like study design and overall. Summary results are given in Table 3.

There was significantly reduced risk of bladder cancer among parous women (summary RR = 0.73, 95% CI: 0.63–0.85; Table 3, Fig. 1A), with no indication of heterogeneity between studies. Summary estimates within strata defined by smoking history reveal the parity–bladder cancer association to be greater among never smokers (summary RR = 0.51, 95% CI: 0.37–0.69) than ever smokers (summary RR = 0.82, 95% CI: 0.56–1.21); between-group $P_{\text{heterogeneity}} = 0.05$; Table 3, Fig. 1B).

Data on OCs show no effect of ever use (summary RR = 0.94, 95% CI: 0.81–1.09; Table 3, Fig. 2A), with no indication of between-study heterogeneity.

Data on any use of HT provide no indication of association with risk (summary RR = 1.01, 95% CI: 0.90–1.13; Table 3, Fig. 2B). Results of 2 studies (23, 24) were clearly outside pseudo 95% confidence limits (not shown; between-study $P_{\text{heterogeneity}} = 0.06$). After excluding these outlying studies, no indication of heterogeneity remained (between-study $P_{\text{heterogeneity}} = 0.95$) and the association remained null (summary RR = 0.96, 95% CI: 0.85–1.07; Table 3).

Data on HT formulation, available for 3 studies, suggested little or no increase in risk following use of E alone (summary RR = 1.14, 95% CI: 0.92–1.40; Table 3, Fig. 2C) but clearly suggest a protective effect of using E + P for HT (summary RR = 0.65, 95% CI: 0.48–0.88; Table 3, Fig. 2D), with the association persisting in summary analysis limited to the 2 published studies (summary RR = 0.68, 95% CI: 0.46–1.00; not shown).

There was no statistical evidence of publication bias in any meta-analysis except for the analysis of any use of HT ($P = 0.02$), but after excluding the 2 outlying studies, the P value for publication bias was no longer significant ($P = 0.14$; Table 3).

Discussion

These analyses revealed a completely consistent pattern of lower UC risk among parous women in the CTS, Shanghai case–control data, and published epidemiologic studies addressing parity. A similar pattern was

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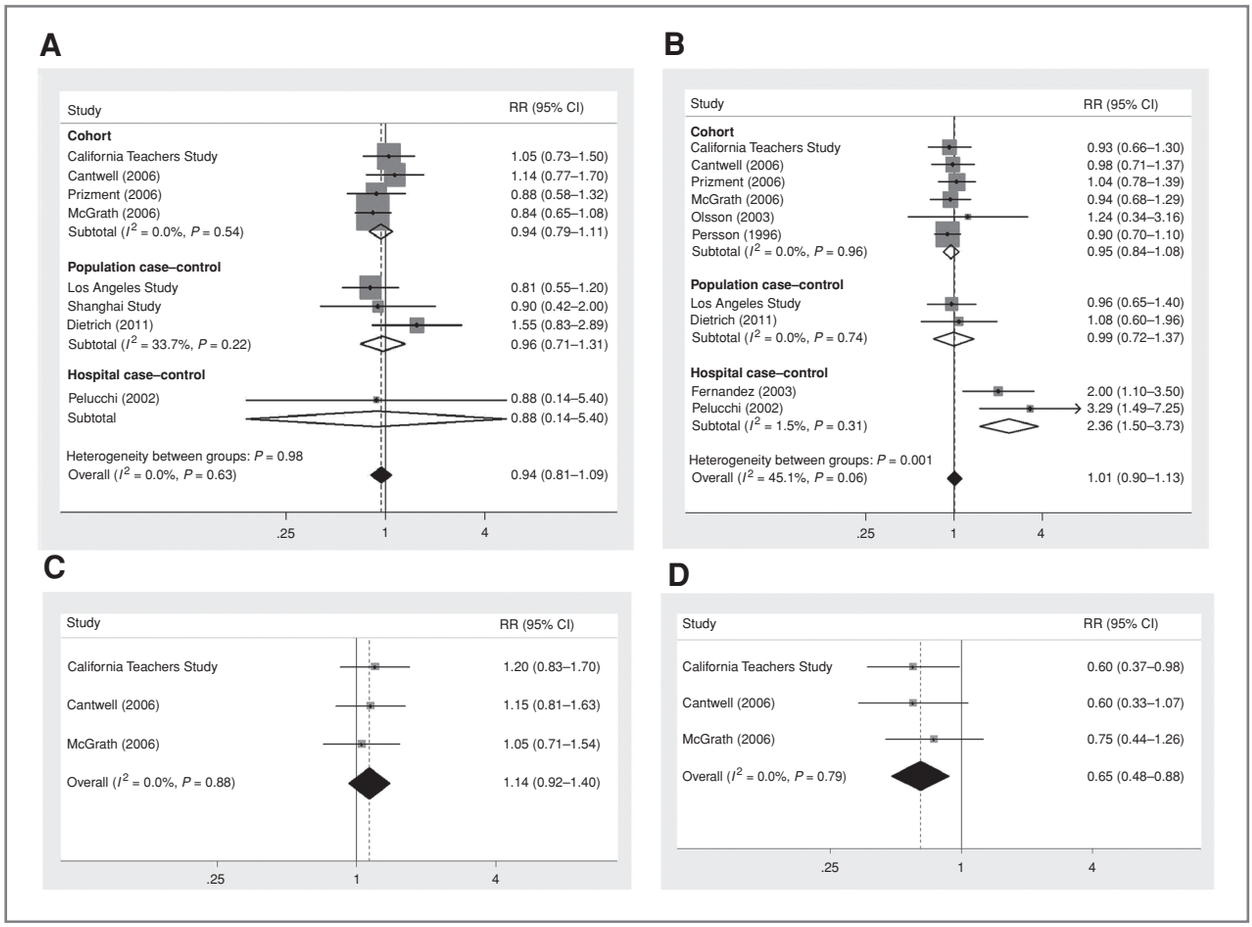

Figure 2. Forrest plots displaying contributing data and results of meta-analyses relating history of exogenous hormone use to risk of bladder cancer, ever versus never use of OCs (A); any menopausal HT (B); estrogen alone for HT (C); and E + P for HT (D). Summary RR (SRR), top and bottom points of diamond; 95% CI of SRR, left and right points of diamond; stratum-specific SRR, open diamond; overall SRR, filled diamond. Individual study RR estimate and 95% CI, point and horizontal line; relative weight, box size.

evident in the LA case–control data, in which births were not measured but history of any pregnancy was associated with lower risk. Published studies examining the parity–UC association (17–19, 21, 25, 27, 29) reported estimates consistent with lower risk among parous women, but most were not statistically significant, likely because of limited numbers of females in individual studies. Most or all reduction in risk may be related to the first birth (or pregnancy), because risk does not seem to depend either on the number of births (or pregnancies) beyond the first or on age at first birth (or pregnancy).

During pregnancy, the bladder undergoes dramatic alterations in structure, function, histology, and gene expression. Steroid hormones may govern these changes, as they can be recapitulated in rodents by treatment with estrogen and progesterone (40), and estrogen and progesterone levels increase dramatically during pregnancy achieving levels unequalled at any other time of a woman's life. However, because mechanisms underlying these changes are not well described, other unrecognized biological processes may mediate any protective effects pregnancy or childbirth confers to the bladder.

Epidemiologic studies previously established that parous women tend to experience lesser risk of cancers of the breast, endometrium, and ovary (41). Studies seeking the biological basis for reduced breast cancer risk years after pregnancy have shown patterns of gene expression that differ between healthy breast tissue of parous and nulliparous women (42, 43). Some differences persist at least a decade after pregnancy and include expression of steroid hormone targets: ERα, ERβ (43), and PR membrane component 2 (42). Thus, persistent, parity-related changes in gene expression may plausibly influence malignant potential of the breast. Future research aimed at identifying pregnancy-related changes in the bladder may similarly provide biological insights into processes responsible for the parity–UC association.

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Table 3. Contributing data and summary RRs and 95% CIs from the meta-analysis of hormonal and reproductive exposures and risk of bladder cancer in women

Exposure	Studies contributing	Cases, *n*	Summary RR	95% CI	$P_{heterogeneity}$[a]	P_{bias}[b]	I^2	Studies outside pseudo 95% confidence limits, *n*
Parity	CTS, Shanghai, 17–19, 21, 25, 27, 29	1,698	**0.73**	**0.63–0.85**	0.64	0.40	0	0
Among never smokers	CTS, Shanghai, 21, 27	468	**0.51**	**0.37–0.69**	0.69	0.17	0	0
Among ever smokers	CTS, Shanghai, 21, 27	326	0.82	0.56–1.21	0.95	0.99	0	0
			$P^c = 0.05$					
Parity excluding study with no smoking adjustment	CTS, Shanghai, 17–19, 21, 27, 29	1,630	**0.71**	**0.61–0.83**	0.76	0.14	0	0
OC use	CTS, LA, Shanghai, 17–19, 22, 29	1,688	0.94	0.81–1.09	0.63	0.22	0	0
Any HT, all studies	CTS, LA, 17–19, 22–24, 28, 29	1,743	1.01	0.90–1.13	0.06	0.02	45	2
HT excluding outlying studies	CTS, LA, 17–19, 24, 28, 29	1,527	0.96	0.85–1.07	0.95	0.14	0	0
HT excluding outlying studies and study with no smoking adjustment	CTS, LA, 17–19, 28, 29	1,469	0.98	0.86–1.13	0.96	0.29	0	0
Estrogen alone for HT	CTS, 17, 19	699	1.14	0.92–1.40	0.88	0.12	0	0
E + P for HT	CTS, 17, 19	699	**0.65**	**0.48–0.88**	0.79	0.60	0	0

[a]Between-study heterogeneity *P* value (studies contributing to each summary RR).
[b]*P* value from Begg's test for publication bias.
[c]*P* value for never smokers versus ever smokers, stratified by study.

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An alternate mechanism whereby pregnancy may reduce risk of developing other cancers is cessation of hormonal cycling, thus lower lifetime number of menstrual cycles. This seems a less likely mechanism in bladder cancer, not only because men—who do not have menstrual cycles—experience greater risk but also because, in women, proxies for cycle number appeared in our analyses to be unrelated to risk. In the CTS, we observed no association with age at menarche, age at menopause, history of breast-feeding, or number of full-term pregnancies; in the CTS, LA, Shanghai, and summary data (17–19, 22, 29), history of OC use was not associated with risk. However, we did not model lifetime number of cycles, and 3 cohort studies previously reported increased bladder cancer risk among women with menopause by age 42 (18) or 45 (17, 19), with 1 result not statistically significant (19).

Two nonhormonal effects of pregnancy on the bladder warrant consideration. First, urinary incontinence, particularly stress incontinence, is reportedly more prevalent among parous women (44), and resulting increases in frequency of urination may in theory reduce bladder cancer risk (45). To address this possibility, we examined frequency of daytime urination as a possible modifier of the parity–UC association in LA case–control data and did not find such modification. A second possibility is that an unrecognized common cause of both UC and infertility could create a spurious association with parity. This might be plausible because the urogenital sinus which gives rise to the bladder, also gives rise to much of the reproductive system. However, in analyses of CTS data in which we excluded from the nulliparous group women who reported inability to achieve pregnancy (24,287 women excluded), a robust association persisted between parity and reduced UC risk (RR = 0.63, 95% CI: 0.44–0.91).

The parity–UC association seems more pronounced among women who never smoked. In Shanghai case–control and CTS cohort data, effects of parity seemed to be stronger among never smokers. This pattern persisted in summary estimates of 4 studies stratified on smoking history, with significant heterogeneity between never smokers versus ever smokers, and was reinforced by a stronger pregnancy–UC association among nonsmokers in LA. It is not clear whether the mechanism whereby parity is associated with reduced risk operates primarily among nonsmokers, or effects of smoking on risk are simply so great that effects of parity are not apparent among smokers. Nonetheless, dramatic effects of parity among nonsmokers suggest that future efforts to understand the biological basis of the parity–UC association may provide long-awaited insights into UC causes among nonsmoking women.

Exogenous hormone exposure was measured by reported use of OCs and menopausal HT. To examine in primary data effects of estrogens alone and E + P used as HT, we relied on the CTS cohort because the use of progestin for HT was not measured in the case–control study. CTS data and meta-analysis of data from 2 cohorts (17, 19) suggest that the use of E + P for HT is associated with a 35% to 40% reduction in bladder cancer risk. The same studies suggest that the use of estrogen alone may be associated with somewhat increased risk, but individual and summary estimates were not statistically significant. Nonetheless, these results led us to question whether null associations estimated for ever versus never use of HT of unspecified formulation in the CTS, LA data, and meta-analysis of 8 studies (17–19, 22–24, 28, 29) may represent a mixture of protective effects of progestin and harmful effects of estrogens, as previously shown for ovarian cancer (46). Statistically significant OR estimates from 2 hospital-based case–control studies (22, 23) exceeded 1.0 but may reflect substantial bias, as articulated by authors of one original report (22); these studies had little influence on the summary estimate. In contrast, ever versus never use of OCs, which contain both estrogen and progestin, was not associated with risk in the CTS, LA, and Shanghai data or meta-analysis of 5 data sets (17–19, 22, 29). A null effect of OC use initially seems at odds with the apparently protective effect of E + P use for HT, as both regimens contain E + P. It may be that effects of E + P later in life are more protective. Alternatively, OC use may influence UC risk, with effects evading detection in these studies due to information bias arising because recall of OC use may be less accurate than that of pregnancy history or recent use of HT, or because ever versus never use does not adequately discriminate between irrelevant and protective durations of exposure. Clearer understanding of any role of exogenous hormones on bladder cancer risk may follow detailed analyses addressing duration, formulation, and schedule of HT use and analyses of OC use by these quantitative measures together with timing of OC use relative to pregnancy and childbirth. Pooled analysis of extant studies may provide considerable insight.

In premenopausal women, progesterone levels change over the menstrual cycle but are highest by far late in pregnancy. At menopause, endogenous levels of estrogen and progesterone decline sharply but HT provides continued exposure to exogenous estrogen and/or progestin. Although PRs are expressed in the human bladder (11, 12), little is known about their function, or that of progesterone or progestins, in this organ. However, one study found that bladder expression of PRs was significantly higher in premenopausal women and postmenopausal women taking HT than in postmenopausal women not using HT (47). It is intriguing to postulate that the action of progesterone and progestins, mediated by PRs, may influence malignant potential of the bladder. However, whether effects of parity are mediated by progesterone and whether any influence of progesterone during reproductive years and progestins in menopause involves common biological processes are questions awaiting mechanistic studies. The possibility that use of progestin as HT may be associated with delayed

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bladder cancer detection, as has been proposed for colorectal cancer (48), also warrants investigation.

Strengths of our primary analyses include use of 2 large, well-designed studies of distinct data structure, with cases limited to UC. Strengths of the case–control study are population-based design, matching of cases and controls on key characteristics, and enrollment of participants from separate populations characterized by high versus low UC incidence. Major strengths of the CTS are the prospective cohort of women followed since 1995 and detailed information on hormonal and reproductive factors.

Each study has several limitations. CTS case numbers were small. Also, hormonal and reproductive data are self-reported and thus subject to misclassification; however, because data were collected prospectively, any misclassification is likely to be nondifferential, with any resulting bias in the direction of no effect. Finally, the cohort consists of public school professionals, limiting generalizability of results. In the case–control study, an analysis of HT constituents was not possible. In Shanghai, there were only 131 cases. In LA, history of any pregnancy was measured rather than history of term pregnancies; we therefore did not include LA data in summary estimates of parity–bladder cancer associations, which were nonetheless robust and supported by the pregnancy–bladder cancer associations from LA data. Recall bias is not likely to have influenced results on parity or pregnancy, as these were not previously regarded as bladder cancer risk factors. As with all analyses, it is possible that some results could be due to chance, but consistency of associations with parity and E + P in all studies addressing these factors is encouraging.

In conclusion, consistent results of epidemiologic studies suggest that parous women experience substantially reduced risk of bladder cancer. Protective effects of parity may arise from the first pregnancy and are particularly evident among nonsmokers. Women who use E + P for HT may also experience reduced risk. Research is now needed to understand the basis of the parity–bladder cancer association and a possible role of steroid hormones in bladder carcinogenesis. Resulting insights may explain why rates among men greatly exceed those among women; have implications for bladder cancer prevention strategies among nonsmokers, who comprise nearly half of incident cases (4); and inform efforts to develop targeted therapies (49).

Disclosure of Potential Conflicts of Interest

Ideas and opinions expressed herein are of the authors and endorsement by the State of California, Department of Health Services, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended, nor should be inferred.

Acknowledgments

We dedicate this report to the memory of our beloved colleague, mentor, and friend, Ronald K. Ross, MD, who long encouraged us to understand UC gender disparity.

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