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Parity, early menopause and the incidence of bladder cancer in women: A case–control study and meta-analysis

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ABSTRACT

Introduction: Incidence rates of bladder cancer are notably higher in men than women. While there is evidence that reproductive and hormonal risk factors may influence risk of bladder cancer, data are inconclusive.

Materials and methods: We examined reproductive, menstrual and hormonal use history in our population-based case–control study of bladder cancer in New Hampshire (NH), USA ($n = 207$ women cases and $n = 463$ women controls). Additionally, we performed a meta-analysis of the published literature. We used unconditional logistic regression analysis to compute adjusted odds ratios associated with each risk factor in the NH study. We combined these estimates with those from the published literature using inverse variance effects models.

Results: In the NH study, a slightly decreased odds ratio was found among women who had ever had a birth compared to nulliparous women and an elevated odds ratio among women who underwent surgical menopause (bilateral oophorectomy), especially at an early age. No overall associations were found with oral contraceptive use or hormone replacement therapy. These findings were generally in agreement with the meta-analytic results for which the combined relative risk (RR) estimate was reduced among ever parous women (combined RR estimate for ever parous versus nulliparous = 0.66, 95% confidence intervals [95% CI] 0.55–0.79) and elevated among those undergoing an early menopause (combined RR estimate for early versus late menopause = 1.59, 95% CI 1.31–1.92). No consistent risk was observed for the other factors.

Discussion: Some reproductive and menstrual factors appear to be related to the incidence of bladder cancer among women; but whether effects are due to female hormones is uncertain.

1. Introduction

Bladder cancer is the most common urologic malignancy in many regions of the world. Several causes have been identified, including tobacco use and certain occupational exposures, and, in particular areas, infectious agents.[1] In general, men experience a two- to fourfold higher risk of bladder cancer than women[2,3], although recent studies suggest

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decreasing mortality trends among men throughout Europe.[4] Prior studies of sex steroid-related factors (i.e. parity, exogenous hormone use, age at menarche and menopause) and bladder cancer risk have yielded varying results. Some, but not all, of these studies suggest that parous women may be at a lower risk than nulliparous women[2,5–11] and that early age at menopause may be related to an increased risk.[2,6,7,9,11,12] An association between oral contraceptives[2,6,7,9] or hormone replacement therapy[2,6–9,13,14] and bladder cancer risk also has been explored previously, but only to a limited extent.

Pregnancy and menopause may cause significant, long-lasting changes in sex steroid levels as well as alterations of bladder tissue and bladder function.[15] In light of the potential role of female sex steroids in bladder cancer etiology, we examined associations between bladder cancer and reproductive factors, oral contraceptive use, hormone replacement therapy, and menopause as part of an ongoing population-based case–control study of bladder cancer conducted in New Hampshire, USA. We further performed a meta-analysis of these factors encompassing the published literature.

2. Materials and methods

2.1. Study group

Through the New Hampshire State Department of Health and Human Services' rapid reporting Cancer Registry, we identified newly diagnosed cases of bladder cancer among New Hampshire residents, aged 25–74 years from 1st July 1994 to 31st December 2001. For efficiency, we shared controls with a study of non-melanoma skin cancer covering a diagnostic period between 1st July 1993 and 30th June 1995 and 1st July 1997 to 30th March 2000 frequency matched to cases by age (25–34, 35–44, 45–54, 55–64, 65–69, 70–74 years) and gender. Additional controls for the intervening period were selected frequency matched to the bladder cancer cases on age (25–34, 35–44, 45–54, 55–64, 65–69, 70–74 years) and gender.[16] Controls less than 65 years of age were randomly selected within age and gender strata using population lists obtained from the New Hampshire Department of Transportation comprised of those with a registered driver's licence. Controls 65 years of age and older were randomly chosen in age and gender strata from data files provided by the Centers for Medicare and Medicaid Services (CMS) of New Hampshire residents enrolled in Medicare, a federal health plan provided to those 65 years of age and older. As described previously, these sources cover over 95% of the population in the age ranges selected for the study.[17]

2.2. Interviews

We conducted standardised personal interviews with the study participants, usually in their home, to obtain information on demographic traits, use of tobacco (including frequency, duration and intensity of cigarette smoking) and other exposures. We requested the original paraffin-embedded tumour specimens for histopathology re-review by the study pathologist who classified tumours according to both WHO 1973 and WHO ISUP criteria.[18] Due to the high overall diagnosis concordance rates (>90%), we classified subjects based on the original pathologist's diagnosis. We obtained informed consent from each participant and all procedures and study materials were approved by the Committee for the Protection of Human Subjects at Dartmouth College.

2.3. Exposure assessment

Participants were asked if they had ever taken oral contraceptives or exogenous hormones other than oral contraceptives (hormone replacement therapy (HRT)) prior to their reference date (for cases, their diagnosis dates and for controls, randomly assigned dates selected from the cases' diagnoses dates to which they were matched). Subjects were classified as ever users, if they had taken oral contraceptives or HRT for at least 3 months, otherwise they were classified as never users. Those who responded positively were asked the year of first use, age at first use, total duration of use and time since their last use of either oral contraceptives or HRT. In addition, participants were asked about their reproductive history including whether they ever had a birth, number of births, and age at first birth. Women also were asked their menopausal status, including whether they were pre- or post-menopausal, age at menopause, and type of menopause, e.g. natural or surgical. For surgical menopause, we elicited whether they had a hysterectomy with or without oophorectomy and number of ovaries removed. To minimise potential reporting bias, we did not reveal the specific hypotheses of interest to either the interviewer or participant, and we did not inform the interviewers of the case–control status of participants.

2.4. Statistical analysis

We computed odds ratios (OR) and their 95% confidence intervals (CI) for bladder cancer risk associated with oral contraceptives (ever versus never use, duration, and time since last use), parity (ever versus never, and number of births), menopause (pre- versus post-menopausal, type and age at menopause), and hormone replacement therapy (ever versus never use) using unconditional logistic regression, taking into account multiple confounding factors.[19] In addition to age, we adjusted for the potential confounding effects of smoking status (current, former, never). Parity was included as a covariate in the models for oral contraceptives, menopause and hormone replacement therapy. We examined all bladder cancers combined as well as invasive and non-invasive tumours separately.

2.5. Meta-analysis

We further conducted a meta-analysis that included prior studies that examined parity (ever/never), use of oral contraceptives (ever/never), use of hormone replacement therapy (ever/never), menopausal status (pre-/post-), and early age at menopause (yes/no). We searched MEDLINE for observational, case–control studies and cohort studies using the following search terms: hormone replacement therapy, oral contraceptives, parity, menopause and bladder cancer. We did not use any language restrictions or other limits in our

search, and we did not attempt to contact authors or editors about unpublished studies. Studies included in the meta-analysis were either cohort or case–control studies published in English that examined relationships between bladder cancer and at least one of the following: parity, oral contraceptive use, menopause status, age at menopause, or hormone replacement therapy use. In the parity analysis, one study was excluded because it only presented data on parous women in the analysis (i.e. did not include nulliparous women as the referent group).[9] A summary of the study characteristics that met the criteria for the meta-analysis is provided in Supplemental Table 1. Published, adjusted relative risk (RR) estimates from each study were combined using an inverse variance fixed effects model or maximum likelihood estimation procedure based on the random effects model if inter-study heterogeneity of estimates was detected.[20,21] To estimate whether individual study estimates were heterogeneous or homogeneous we computed a Q-statistic and applied the chi-square test.[22]

In studies that did not examine variables of interest dichotomously, the RR estimates and their CIs based on categorical data were converted to those for dichotomous variables (e.g. we converted estimates based on number of births into those for nulliparous versus parous). We then used the crude estimates to calculate combined risk estimates of the dichotomous variables. While different cut points were used for age at menopause across studies, they were similar. Therefore, we compared the youngest age group to the oldest age group evaluated in each study. Additionally, in the study by Huang and colleagues[11], the youngest age at menopause was compared to the second tertile; in order to keep the direction of comparisons uniform, we calculated the crude odds ratio comparing the youngest group to the oldest group for this study.

3. Results

A total of 207 cases and 463 control women were included in the study and asked about their number of offspring. As questions for women were added after the initiation of interviews in the parent study[23], 207 cases and 364 controls were administered questions on oral contraceptive and hormone replacement therapy use, and menopause.

Overall, cases were more likely to be current or former smokers than controls, but were comparable with respect to

Table 1 – Selected characteristics of women bladder cancer cases and controls.

	Controls[a]		Bladder cancer cases[b]	
	n	%	*n*	%
Total subjects	331	100	187	100
Age				
<55	98	30	51	27
55–63	78	24	46	25
64–68	64	19	34	18
⩾69	91	27	56	30
Smoking				
Never	151	46	50	27
Former	126	38	62	33
Current	54	16	75	40
Pack-years				
⩽32	129	73	66	49
>32	48	27	68	51
Education				
High school or technical college	173	53	135	73
College	106	32	40	22
Graduate or professional school	49	15	10	5
Family history of bladder cancer				
No	318	99	159	93
Yes	4	1	12	7
Histology				
Transitional	–	–	170	96
Non-transitional	–	–	8	4
Stage				
CIS	–	–	1	1
Non-invasive low grade	–	–	112	69
Non-invasive high grade	–	–	8	5
Invasive	–	–	41	25

[a] Three controls missing data on education, nine missing data on family history.
[b] Two cases missing data on education, 16 missing data on family history, nine missing transitional case status, 25 missing bladder cancer stage.

age. Cases also were more likely to have a family history of bladder cancer and not have education beyond high school or technical college (Table 1).

A reduced odds ratio was observed for women who had had a birth (OR = 0.71, 95% CI 0.40–1.26) compared to women who had never had a birth (Table 2). However, the confidence intervals were wide, and the risk estimates did not change appreciably with an increasing number of births (Table 2). Further, these results did not appear to differ significantly between invasive (OR = 0.78, 95% CI 0.27–2.23) and non-invasive (OR = 0.67, 95% CI 0.35–1.28) tumours. Forty-two percent of cases and 43% of controls reported a history of oral contraceptive use. The adjusted odds ratio for ever use of oral contraceptives was modestly elevated (OR = 1.55, 95% CI 0.83–2.89), and was elevated specifically among those who last used oral contraceptives 25 or more years ago (OR = 2.13, 95% CI

Table 2 – Adjusted odds ratios (95% confidence intervals) for parity, oral contraceptive use, menopausal status and hormone replacement therapy use among women cases and controls.

	Controls[c]		Bladder cancer cases[d]		
	n = 379	%	*n* = 197	%	OR[a] (95% CI)
Number of births					
None	39	10	23	6	1.00 (reference)
Some	340	90	174	46	0.71 (0.40–1.26)
1–2	161	47	78	23	0.67 (0.36–1.24)
3–4	132	39	71	21	0.75 (0.40–1.39)
⩾5	47	14	25	7	0.74 (0.35–1.57)
p for trend					0.632
Oral contraceptive use					
Never	188	57	108	58	1.00 (reference)
Ever	143	43	79	42	1.55 (0.83–2.89)
Total duration of use					
No use	188	57	108	59	1.00 (reference)
3 months – 2 years	43	13	29	16	1.70 (0.77–3.79)
3–6 years	46	14	13	7	0.87 (0.31–2.46)
7 years or more	52	16	33	18	1.73 (0.81–3.73)
p for trend					0.259
Time since last use					
No use	188	57	108	58	1.00 (reference)
25 or more years	41	12	40	21	2.13 (1.08–4.20)
0–24 years	102	31	39	21	0.82 (0.35–1.92)
p for trend					0.91
Menopause status					
Premenopausal	68	21	26	14	1.00 (reference)
Postmenopausal	262	79	160	86	1.30 (0.45–3.77)
Natural	156	60	95	59	0.84 (0.21–3.39)
Surgical (bilateral oophorectomy)	48	18	31	19	2.80 (0.65–12.05)
Age at menopause[b]					
⩾45 years	158	65	99	63	1.00 (reference)
<45 years	85	35	59	37	1.33 (0.72–2.47)
Age at natural menopause[b]					
⩾45 years	124	86	79	83	1.00 (reference)
<45 years	20	14	16	17	0.73 (0.21–2.54)
Age at bilateral oophorectomy[b]					
⩾45 years	23	50	10	33	1.00 (reference)
<45 years	23	50	20	67	5.37 (1.20–23.93)
Hormone replacement therapy use[b]					
Never	151	58	101	64	1.00 (reference)
Ever	110	42	58	36	1.08 (0.60–1.96)

[a] Adjusted for age and smoking status.

[b] Restricted to post-menopausal women only.

[c] 48 Controls missing data on oral contraceptive use, two missing data on duration of oral contraceptive use, 49 missing data on menopausal status, 19 missing data on age at menopause, 12 missing age of natural menopause, two missing age at bilateral oophorectomy, one post-menopausal women missing data on hormone replacement therapy (HRT) use.

[d] 10 Cases missing data on oral contraceptive use, four missing data on duration of oral contraceptive use, 11 missing data on menopausal status, two missing data on age at menopause, one missing age of bilateral oophorectomy, one post-menopausal women missing data on HRT use.

1.08–4.20); however, there was no overall trend by duration of use (p for trend = 0.259) (Table 2). Additionally, the association with ever use of oral contraceptives did not appear to differ between invasive (OR = 1.34, 95% CI 0.45–3.94) and non-invasive (1.47, 95% CI 0.70–3.10) tumours.

The odds ratio for bladder cancer was elevated among post-menopausal compared with pre-menopausal women, particularly among those who underwent a surgically-induced menopause (i.e. bilateral oophorectomy) (OR = 2.80, 95% CI 0.65–12.05) (Table 2). We found an increased odds ratio associated with early age at menopause (<45 years versus ⩾45 years) (OR = 1.33, 95% CI 0.72–2.47), and this was most evident among those with an early surgical menopause (OR = 5.37, 95% CI 1.20–23.93) (Table 2). Odds ratios for early surgical menopause were likewise similar between invasive (OR = 4.00, 95% CI 0.28–56.65) and non-invasive (OR = 4.69, 95% CI 0.59–37.29) tumours. When adjusted for smoking pack years, the estimate only increased (OR = 8.25, 95% CI 1.15–59.24), however with more limited statistical precision. A similar percentage of cases and controls reported a history of hormone replacement therapy (OR = 1.08, 95% CI 0.60–1.96), and associations did not differ by type of menopause (data not shown).

Meta-analysis results also indicated a decreased odds ratio with ever having had a birth (combined RR estimate = 0.69, 95% CI 0.57–0.82, based on eight studies[2,5–8,10,11]) without evidence of heterogeneity between studies (Chi-square for heterogeneity = 7.12, p = 0.42) (Fig. 1). An increased odds ratio was observed with an early age at menopause (combined RR estimate = 1.49, 95% CI 1.25–1.78, based on seven studies[2,6,7,9,11,12]), again without evidence of inter-study heterogeneity (Chi-square for heterogeneity = 6.23, p = 0.40) (Fig. 2). While the summary RR estimate was increased slightly for ever use of HRT (combined RR estimate = 1.27, 95% CI 1.03–1.57, based on seven studies[2,6,7,9,13,14]), there was evidence of heterogeneity (Chi-square for heterogeneity = 12.30, p = 0.06). The summary estimate for ever use of oral contraceptives was close to one (combined RR estimate = 0.95, 95% CI 0.66–1.37, based on five studies[2,6,7,9], Chi-square for heterogeneity = 4.17, p = 0.38) and was modestly elevated for menopausal status, but with wide confidence intervals (combined RR estimate = 1.42, 95% CI 0.88–2.26, based on five studies[2,6,9,11], Chi-square for heterogeneity = 4.85, p = 0.30).

4. Discussion

In our population-based case–control study parous women appeared to be at a lower risk of developing bladder cancer than nulliparous women. However, our individual study risk estimates were imprecise, and we did not observe a trend with number of births. We found evidence of an increased risk of bladder cancer for post-menopausal women compared to pre-menopausal women, particularly in women who underwent a bilateral oophorectomy at an early age (<45 years). We did not find any overall association between use of hormone replacement therapy or oral contraceptives.

It is possible that our findings were due to chance, unmeasured confounding or other biases. For example, detection bias is possible in women who have undergone a bilateral oophorectomy if the reason was for cancer or another condition resulting in increased surveillance. An important limitation of our study is statistical power; while our study population was relatively large, we had a relatively small group of women. For this reason, we considered our findings along with others by conducting a meta-analysis.

Indeed, a number of prior studies have investigated reproductive history, menopause and sex steroid use in relation to bladder cancer among women. Consistent with ours, nearly all prior studies observed an inverse association between parity and bladder cancer risk.[5,8,11] Our meta-analysis showed a

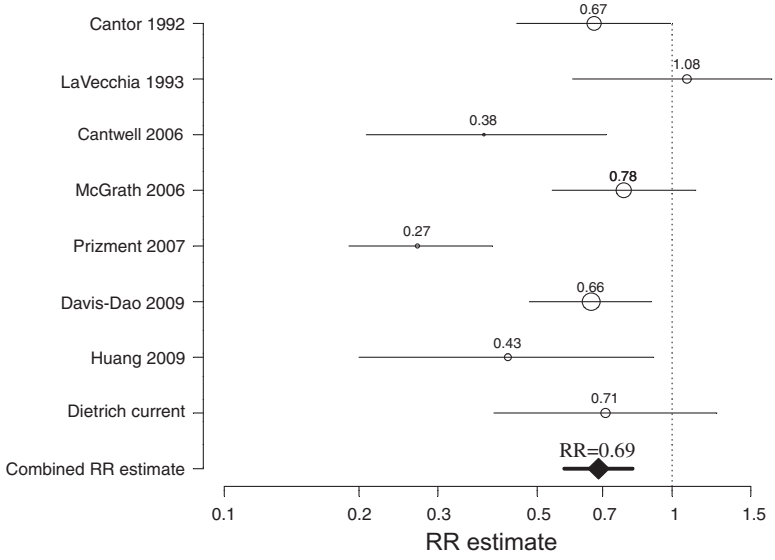

Fig. 1 – Meta-analysis forest plot of parity and bladder cancer risk in women. For individual studies, the centre of the circle represents the individual study relative risk estimate and the radius of the circle being proportional to the weight of the study relative risk estimate in the summary relative risk (RR) computation (reciprocal of the variance).[20–22] The line represents the confidence interval. The combined RR estimate derived from the meta-analysis is represented by a diamond, with the 95% confidence interval represented by the bold line.

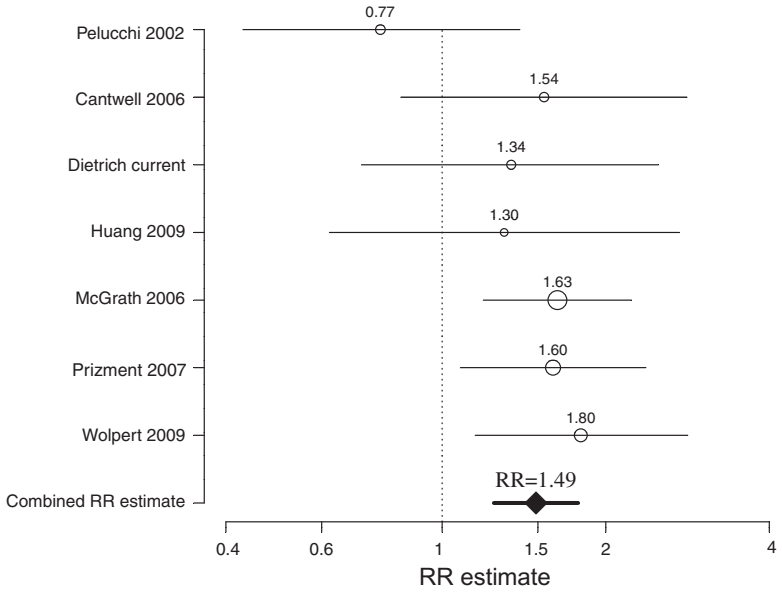

Fig. 2 – Meta-analysis forest plot of early menopause and bladder cancer risk in women. For individual studies, the centre of the circle represents the individual study relative risk estimate and the radius of the circle being proportional to the weight of the study relative risk estimate in the summary relative risk (RR) computation (reciprocal of the variance).[20–22] The line represents the confidence interval. The combined RR estimate derived from the meta-analysis is represented by a diamond, with the 95% confidence interval represented by the bold line.

decrease in risk with parity irrespective of study design. Interestingly, prior studies have not found trends of decreasing risk with increasing number of births[2,6,7,9,10] as opposed to findings for breast cancer, for example, in which risk is lower with each additional birth.[24]

In agreement with our study, prior studies indicated no overall association with ever use of oral contraceptives.[2,6,7,9] Cantwell and colleagues[6] and McGrath and colleagues[2] further examined the effect of duration of oral contraceptive use in relation to bladder cancer risk and found no association. Our data suggested an elevated risk among those who used oral contraceptives in the distant past, but to our knowledge no prior studies examined time since last use. Thus, this finding would need to be confirmed or refuted in future research.

Recent data indicate that risk of bladder cancer may be influenced by menopause. The US Nurses' Health Study reported a twofold increase in risk for women who experienced a natural or surgical menopause compared to those who had not undergone menopause[2], and others have observed similar trends.[6,9] In contrast, a recent study by Huang and colleagues[11], found a reduced odds ratio among post-menopausal women, however with wide confidence intervals. Another study that specifically examined bilateral oophorectomy found an increased bladder cancer risk among these women compared to women who did not undergo a bilateral oophorectomy.[7] In at least three studies, younger menopause (<45 years old) was associated with an increased risk[2,7,12]; in two studies relative risk estimates tended to be elevated for women in the oldest age at menopause category[7,10], but the results were not statistically significant, and in one, the association was inversed.[6,9,11] In the New Hampshire population, we observed an increased risk primarily with younger age at bilateral oophorectomy, and a more modest increase with a younger age at menopause overall. In our meta-analysis, the summary relative risk estimate was increased for early versus late age at menopause, and results appeared fairly consistent across studies. Hence, the underlying reasons for this observation may deserve further inquiry.

Studies investigating hormone replacement therapy use in relation to bladder cancer risk have been inconsistent. Two case–control studies (106 and 110 cases respectively) found two- to threefold higher risks of bladder cancer among ever users of hormone replacement therapy compared to never users, as well as a pattern of increasing risk with duration of use.[9,13] In addition to the present New Hampshire population-based study, four published cohort studies reported no association with ever use of hormone replacement therapy.[2,6–8] Only two of these studies examined the potential difference between combined oestrogen–progesterone treatments and oestrogen alone, and neither found a difference between therapy types.[2,8] Further, one Swedish cohort study found no association among all women, but a decreased risk among smokers who had used hormone replacement therapy.[14] As a result of the various types of HRT regiments that were used in each study, we were not able to examine a homogeneous exposure. Thus, further research will need to resolve whether an association exists.

The reasons for higher incidence of bladder cancer among men than among women remain elusive, and whether sex steroids play a role in bladder cancer etiology is likewise unclear. Urothelial cells contain oestrogen and progesterone receptors and are hormone responsive.[25–28] Moreover, oestrogens inhibit and androgens increase the growth and development of bladder malignancies in animal models.[29–31] Decreasing levels of oestrogen in post-menopausal women

have been associated with bladder dysfunction (e.g. incontinence) and recurring urinary tract infections[15,32], which in turn could increase bladder cancer risk in women.[2] Future research to elucidate the potential mechanism of sex steroids on bladder carcinogenesis may provide insights as to why factors that affect endogenous sex steroids (e.g. parity and timing of menopause) have been repeatedly associated with risk of bladder cancer in epidemiologic studies. Finally, in light of the small number of women in individual studies, larger efforts will be required to understand whether sex-steroid related factors play a role in the development of bladder malignancies.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.10.007.

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