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Reproductive factors, exogenous hormone use and bladder cancer risk in a prospective study

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Sex is a consistent predictor of bladder cancer: men experience 2–4-fold higher age-adjusted rates than women in the U.S. and Europe. The objective of this study was to examine whether hormone-related factors are associated with bladder cancer in women. We examined parity, age at menarche, age at first birth, age at menopause, oral contraceptive use and menopausal hormone therapy (HT) use and bladder cancer risk in the Breast Cancer Detection Demonstration Project Follow-Up Study. Endpoint and exposure information was collected on 54,308 women, using annual telephone interviews (1980–86) and 3 mailed, self-administered questionnaires (1987–98). During an average follow-up time of 15.3 years, 167 cases of bladder cancer were identified. Univariate and adjusted rate ratios (RRs) were estimated using Poisson regression. Parity, age at menarche, age at first birth, age at menopause, and oral contraceptive use were not associated with bladder cancer risk. The majority of menopausal women who took HT used estrogen therapy (ET). Postmenopausal women with less than 4, 4–9 years, 10–19 years and 20 or more years of ET use had RRs of 1.55 (95% CI = 0.96–2.51), 1.00 (95% CI = 0.49–2.04), 1.23 (95% CI = 0.62–2.43) and 0.57 (95% CI = 0.14–2.34), respectively, compared with nonusers (p = 0.50). Findings from this study are not consistent with the hypothesis that hormone-related factors in women are associated with bladder cancer.

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Key words: bladder cancer; hormone therapy; reproductive factors; estrogen; parity; age at menarche; menopause

In 2001, the U.S. age-adjusted incidence rates (per 100,000 persons) for bladder cancer were 37.1 in men and 9.4 in women.1 Sex is a consistent predictor of bladder cancer: men experience 2–4-fold higher rates than women in the U.S. and Europe.2,3 Greater exposure to established environmental risk factors, such as industrial exposures2 and cigarette smoking,3 in men explains some, but not all, of the higher risk.6 The reduced risk in women may be explained in part by hormones or correlates of hormonal status, such as age at menarche, parity or age at menopause.6

Evidence from animal studies suggests that sex hormones play an important role in bladder cancer etiology,7,8 but few human studies have addressed the potential association between reproductive factors and bladder cancer.9 Three population-based ecologic studies10–12 reported lower bladder cancer incidence or mortality rates among parous women than nulliparous women. Case-control studies reported reduced risks in parous women, which were stronger among never-smokers, and increased risks in menopausal hormone therapy users.11,14 Recent findings suggest that menopausal status and age at menopause may play a role in modifying bladder cancer risk among women.15 Postmenopausal women, compared with premenopausal women, were at increased risk (incidence rate ratio = 1.93, 95% CI 0.99–3.78). For postmenopausal women, early menopause (≤45 years), compared with late menopause (≥50 years), was associated with a statistically significant increased risk of bladder cancer (incidence rate ratio = 1.63, 95% CI 1.20–2.23).

Outside the hypothesized environmental risk factor differences, the reason for lower bladder cancer incidence rates in women compared with that in men remains largely unexplained. We therefore examined reproductive factors, oral contraceptive use and postmenopausal hormone use, and risk of bladder cancer in the Breast Cancer Detection and Demonstration Project (BCDDP) Follow-up Study.

Material and methods

Study population

In 1979, the National Cancer Institute (NCI) established a follow-up study of 64,182 of the 283,222 original BCDDP participants. The study included women from all 29 screening centers in 27 cities16 and consisted of 4,275 women from the BCDDP who were diagnosed with breast cancer, 25,114 women who had breast surgery with no evidence of malignant disease, 9,628 women who were recommended for surgical consultation during the screening, and a sample of women who had neither surgery nor recommendation for surgical consultation (n = 25,165).17 Institutional Review Boards at the NCI and participating clinics approved the study. All participants provided informed consent.

Cohort follow-up

Data collection occurred in 4 phases. 61,430 (96%) of the invited cohort agreed to participate and completed a baseline interview, Phase 1 (1980–1986), which included up to 6 (usually 4) annual telephone interviews. During Phases 2 (1987–1989), 3 (1993–1995) and 4 (1995–1998), participants were mailed single, self-administered questionnaires. Nonrespondents to the mailed questionnaires were interviewed by telephone, if possible.

Exposure ascertainment

Demographic (e.g., education, ethnicity and income) and reproductive (e.g., age at menarche, age at first live birth, menopausal status and parity) data were collected during Phase 1. Menopausal status and gynecologic surgery data were queried at each phase. Height and weight were measured during the original screening project (1973–1979). Oral contraceptive data, including duration of use and age at first use of birth control pills, was collected at Phase

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1 only. Menopausal hormone therapy (HT) use, including formulation, ages at first and last use, and duration, was collected at each phase, as previously described.\(^{16,17}\) Smoking status and history, including years smoked, smoking intensity, and ages started and stopped, were obtained on the Phase 2 questionnaire and updated during Phase 3.

**Cancer ascertainment**

Each questionnaire asked participants about cancer diagnoses since their last interview. We verified reported bladder cancer diagnoses [ICD codes 188.x (ICDO-1) and C67.x (ICDO-2)] through medical record review. The cohort was linked against the National Death Index (NDI) to identify deaths and cause of death during follow-up. In 1999–00, we also linked 44,139 women (72% of baseline interview respondents; 85% of Phase 2 respondents) to state cancer registries, using the state of participants’ last-known address, to identify additional cancer diagnoses. We identified 167 bladder cancers: 105 were confirmed (72% of baseline interview respondents; 85% of Phase 2 respondents) via pathology reports or medical records, 29 via linkage with state cancer registries, and 25 via linkage with the NDI; 18 were based only on self-report. When medical records were available for review, 99% of self-reported cancers were confirmed. Nineteen of the 29 registry-based bladder cancers were not reported by study participants. If we set a similar level of false-negative reporting among the 15,501 women in this analysis who were not linked to state cancer registries, then we estimate our combined ascertainment methods identified 95% of all incident bladder cancers in this study population during the study period.

**Analytic data set**

After excluding women with a missing date of death (N = 5), reported a diagnosis of bladder cancer (N = 43) or another primary cancer (N = 3,070) before baseline (including breast cancers identified during the BCDDP), or reported a bladder cancer diagnosis with an undated date (N = 4), the analysis included 54,308 women. The numbers of women who subsequently completed Phases 2, 3 and 4 questionnaires were 45,863 (84%), 40,052 (74%) and 38,147 (70%), respectively. Death, (N = 1,336, 2.5%), refusal (N = 2,007, 3.7%), illness or inability to contact the woman before the end of the questionnaire period (N = 1,953, 3.6%) and incomplete questionnaires (N = 3,149, 5.8%) accounted for missing Phase 2 questionnaires. Respectively numbers for missing Phase 3 and Phase 4 questionnaires were 4,535 (8.4%), 555 (2.9%) 1,077 (2.0%) and 7,089 (13.1%); and 6,886 (12.7%), 2,406 (4.4%), 3,045 (5.6%) and 824 (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%). At the end of follow-up, endpoint status was known for 86.9% of the 54,308 women: 72.7% were censored at the Phase 4 questionnaire period (7.0%).

**Statistical analysis**

Person-time was computed for each participant from her base-line interview date until the date of a bladder cancer diagnosis, death or completion of a Phase 4 questionnaire, whichever came first.\(^{18}\) For women who did not respond to the Phase 4 questionnaire, person-time was computed until the date of last contact (e.g., a notice of refusal to participate) or the estimated date they would have completed the Phase 4 questionnaire. Based on the NDI and cancer registry linkages, we assumed that women without a Phase 4 questionnaire were alive and disease-free.\(^{19}\)

Time-dependent covariates for age, calendar time, menopausal status, smoking and HT use were updated at 1-year intervals. To analyze smoking and HT use in a time-dependent manner, periods of use were reconstructed using reported dates of exposure.

Poisson regression modeled the rate of developing bladder cancer during follow-up and generated rate ratios (RRs) with 95% confidence intervals (CIs) for categorized variables, using standard likelihood ratio methods\(^{20}\) in EPICURE software.\(^{21}\) Potential confounding was assessed by evaluating parameter estimate changes before and after the addition of variables associated with both exposures and bladder cancer. Adjusted and unadjusted RRs were generally similar. We present the adjusted models, which included stratification on age (5-year intervals), calendar time (5-year intervals) and smoking status (current, former, never smoker). Because smoking is a strong bladder cancer risk factor, we also considered smoking duration, but adjustment for both status and duration\(^{22}\) did not change the results. We therefore present the more parsimonious models based on smoking status only.

**Results**

The cohort accrued 338,502 person-years of follow-up. The mean ± SD ages (in years) at entry and exit were 55.4 ± 8.8 and 70.6 ± 8.4, respectively. The mean ± SD follow-up times were 15.3 ± 2.8 years and 9.8 ± 4.2 years for censored women and women who developed bladder cancer, respectively. Table I shows descriptive characteristics of the analytic population.

There was no association between bladder cancer and age at menarche or age at first birth (Table II). Parous women had a statistically nonsignificant reduced risk compared with nulliparous women (RR 0.82; 95% CI 0.56–1.20), but we observed no trend with increasing parity. The null association with parity did not change after stratification by smoking status (data not shown). Compared with natural menopause at 50–53 years, both earlier

<table>
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<tr>
<th>Age (years)</th>
<th>Cancers</th>
<th>Person-years</th>
<th>RR (^{1})</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>&lt;18.5</td>
<td>2</td>
<td>7,469</td>
<td>0.55</td>
<td>0.14–2.24</td>
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<tr>
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<td>25</td>
<td>103</td>
<td>214,102</td>
<td>1.00</td>
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<tr>
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<td>142</td>
<td>42</td>
<td>78,414</td>
<td>1.05</td>
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<tr>
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<table>
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<th>Person-years</th>
<th>RR (^{1})</th>
<th>95% CI</th>
</tr>
</thead>
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<td>1.00</td>
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<tr>
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<td>36,402</td>
<td>1.81</td>
<td>1.13–2.89</td>
</tr>
</tbody>
</table>

1Adjusted for age, calendar year and smoking status (never, former or current) except for age RRs (adjusted for calendar year and smoking) and Smoking RRs (adjusted for age and calendar year).--Time dependent variables.

**TABLE I – DESCRIPTIVE CHARACTERISTICS OF THE WOMEN IN THE BCDDP FOLLOW-UP STUDY**

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**REPRODUCTIVE FACTORS AND BLADDER CANCER RISK**

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Factors, exogenous hormones, and bladder cancer. Early reproductive events, such as age at menarche, age at first birth and parity, were not associated with bladder cancer. Both older (≥54 years) and younger (<45 years) ages at natural menopause appeared to similarly increase risk, compared with menopause at 50–53 years, but only the former was statistically significant. Neither type nor duration of exogenous hormone use was associated with bladder cancer.

Previous studies offer inconsistent data on these potential associations. In an Italian case–control study that included 110 cases and 298 controls, Pelucchi et al. reported that both ever-use (OR = 3.29, 95% CI 1.49–7.25) and increasing duration of HT use were significantly associated with bladder cancer. They mentioned detection factors, exogenous hormones, and bladder cancer. Early reproductive events, such as age at menarche, age at first birth and parity, were not associated with bladder cancer. Both older (≥54 years) and younger (<45 years) ages at natural menopause appeared to similarly increase risk, compared with menopause at 50–53 years, but only the former was statistically significant. Neither type nor duration of exogenous hormone use was associated with bladder cancer.

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bias as a possible explanation for those associations, because post-menopausal bleeding in HT users may facilitate surveillance for other medical conditions.23 Persson et al.24 found no relationship with menopausal HT in a Swedish record-linkage study. The population-based cohort of Olsson et al.25 showed bladder cancer risk among smokers was decreased for those who ever used HT compared with that for those who did not. In our study, most of the associations with these potential risk factors were null, or could be due to chance.

The reported frequencies of exogenous hormone use generated 90% power (using a two-sided α = 0.05) to detect a RR of 0.50 for unopposed ET and 80% power to detect a RR of 0.50 for oral contraceptive use. Yet, even our relatively large cohort, which was followed for 20 years, had lower statistical power for other potential associations. We therefore cannot rule out smaller increased or decreased risks. Potential unmeasured confounding is another limitation: we lacked information on other hypothesized risk factors, such as urinary tract infections,26,27 micturition,28 hair dyes29 or pesticides.30

There are several strengths to our study. We updated time-varying exposure information throughout follow-up and assessed exposures collected prior to bladder cancer diagnosis. Previous analysis of HT17,18 in BCDDP are consistent with the small increased relative risks noted in other studies, which argues against significant HT exposure misclassification. Other studies have shown that self-reported oral contraceptive use and recall of self-reported reproductive factors, such as ages at menarche and menopause, are reproducible and generally valid.31,32 Finally, the significantly increased risks among smokers suggest good internal validity in our data.

In summary, our study does not support the hypothesis that differences in hormone-related factors in women are associated with bladder cancer risk. No specific factors other than smoking were associated with bladder cancer in our data. Further investigations into other potential explanations for the difference in bladder cancer risk between men and women are needed.

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