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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 years, 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.

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.13,14 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 1.20–2.25).

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 and age at first use of birth control pills, was collected at Phase

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Cancer ascertainment

Each questionnaire asked participants about cancer diagnoses since their last interview. We verified reported bladder cancer diagnoses [ICD codes 188.x (ICD-O-1) and C67.x (ICD-O-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 available state cancer registries, using the state of participation. In 1999–00, we also linked 44,139 women (72% of baseline interview respondents; 85% of Phase 2 respondents) to available state cancer registries, using the state of participation. We verified reported bladder cancer diagnoses through medical record review. We also linked 44,139 women to available state cancer registries, using the state of participation. We verified reported bladder cancer diagnoses through medical record review. We also linked 44,139 women (72% of baseline interview respondents; 85% of Phase 2 respondents) to available state cancer registries, using the state of participation.

We identified 167 bladder cancers: 105 were confirmed via pathology reports or medical records, 29 via linkage with state cancer registries, and 25 via linkage with the NDI. We were only able to contact 18 of these women by telephone. If we had been able to contact all of them, we would have completed at least some follow-up. In 1999–00, we also linked 44,139 women (72% of baseline interview respondents; 85% of Phase 2 respondents) to available state cancer registries, using the state of participation.

Analytic data set

After excluding women with a missing date of death (N = 5), 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 undetermined date (N = 4) after death, the analysis included 54,308 women. The number 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. The number 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. The number 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. The number 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. The number 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.

Statistical analysis

Person-time was computed for each participant from her baseline interview date until the date of a bladder cancer diagnosis, death or completion of a Phase 4 questionnaire, whichever came first. 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.

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. 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.

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).

Table I – Descriptive characteristics of the women in the BCDDP follow-up study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Cancers</th>
<th>Person-years</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td>2</td>
<td>28,609</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>18.5 to &lt; 25</td>
<td>103</td>
<td>214,102</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>25 to &lt; 30</td>
<td>42</td>
<td>78,414</td>
<td>1.05</td>
<td>0.73–1.50</td>
</tr>
<tr>
<td>30 to &lt; 35</td>
<td>14</td>
<td>22,348</td>
<td>1.28</td>
<td>0.73–2.25</td>
</tr>
<tr>
<td>≥ 35</td>
<td>3</td>
<td>8,142</td>
<td>0.83</td>
<td>0.26–2.63</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>8,026</td>
<td>0.79</td>
<td>0.25–2.50</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>62</td>
<td>172,600</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30</td>
<td>48,780</td>
<td>2.44</td>
<td>1.56–3.80</td>
</tr>
<tr>
<td>Former smoker</td>
<td>50</td>
<td>807,199</td>
<td>1.60</td>
<td>1.16–2.46</td>
</tr>
<tr>
<td>Unknown</td>
<td>25</td>
<td>3,6400</td>
<td>1.81</td>
<td>1.13–2.89</td>
</tr>
<tr>
<td>Smoking duration (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>62</td>
<td>172,600</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>8</td>
<td>36,914</td>
<td>0.73</td>
<td>0.35–1.53</td>
</tr>
<tr>
<td>20–39</td>
<td>38</td>
<td>67,371</td>
<td>1.95</td>
<td>1.29–2.93</td>
</tr>
</tbody>
</table>

1Adjusted for age, calendar year and smoking status (never, former or current) except for age RR (adjusted for calendar year and smoking) and Smoking RRs (adjusted for age and calendar year).
unknown parity accounted for 162 person-years. Unknown age at first birth accounted for 458 person-years. Unknown menopausal status accounted for 30 person-years.

The majority of use was unopposed hormone therapy (HT) and bladder cancer. Women who smoked for 40 years or more had a RR of 2.44 (95% CI 1.96–3.08) compared with never-smokers (OR 0.30–0.88); parity was not associated with bladder cancer among postmenopausal women only. Among post menopausal women who used ET only; excludes women whose duration of use was unknown.

Discussion

This prospective study of 54,308 women who were followed for almost 20 years produced no associations between reproductive 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 significantly 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. found no significant associations between bladder cancer and menstrual and reproductive factors, including parity and late age at first birth. An earlier case–control study by Cantor et al. in Iowa showed an inverse association with parity (adjusted OR = 0.67, 95% CI 0.44–1.00, for parous vs. nulliparous) that was restricted to women who had never smoked before (OR = 0.51, 95% CI 0.30–0.88); parity was not associated with bladder cancer among ever-smokers (OR = 0.93, 95% CI 0.49–1.77). We did not replicate those findings.

More recently, McGrath et al. showed that 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). We also showed an increased risk for women with an earlier menopause although this was not statistically significant (RR = 1.53, 95% CI 0.82–2.82). There were however only 15 cases in this younger age category in our study compared with 7 in the study of McGrath et al.

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

### Table II – Reproductive Factors and Bladder Cancer Risk in the BCDDP

<table>
<thead>
<tr>
<th>Menopausal status/type</th>
<th>Cancers</th>
<th>Person-years</th>
<th>RR (^1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>103</td>
<td>168,220</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Surgical</td>
<td>32</td>
<td>56,501</td>
<td>1.04</td>
<td>0.70–1.55</td>
</tr>
<tr>
<td>Unknown Status</td>
<td>28</td>
<td>90,084</td>
<td>0.64</td>
<td>0.42–0.97</td>
</tr>
<tr>
<td>Other Type</td>
<td>3</td>
<td>1,949</td>
<td>2.20</td>
<td>0.70–6.96</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1</td>
<td>21,693</td>
<td>0.27</td>
<td>0.03–2.07</td>
</tr>
<tr>
<td>Age at natural menopause (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>15</td>
<td>16,200</td>
<td>1.53</td>
<td>0.82–2.92</td>
</tr>
<tr>
<td>45–49</td>
<td>32</td>
<td>57,784</td>
<td>1.06</td>
<td>0.65–1.71</td>
</tr>
<tr>
<td>50–53</td>
<td>36</td>
<td>71,182</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>&gt;54</td>
<td>20</td>
<td>23,024</td>
<td>1.59</td>
<td>0.92–2.77</td>
</tr>
</tbody>
</table>

### Table III – Oral Contraceptive and Hormone Therapy Use and Bladder Cancer Risk in the BCDDP Follow-up Study

<table>
<thead>
<tr>
<th>Hormone therapy use</th>
<th>Cancers</th>
<th>Person-years</th>
<th>RR (^1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used oral</td>
<td>125</td>
<td>231,728</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Ever used oral</td>
<td>41</td>
<td>105,484</td>
<td>1.14</td>
<td>0.77–1.70</td>
</tr>
<tr>
<td>Duration of use (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>21</td>
<td>48,303</td>
<td>1.25</td>
<td>0.76–2.04</td>
</tr>
<tr>
<td>2–5</td>
<td>14</td>
<td>26,652</td>
<td>1.56</td>
<td>0.87–2.78</td>
</tr>
<tr>
<td>&gt;5</td>
<td>6</td>
<td>30,529</td>
<td>0.59</td>
<td>0.25–1.37</td>
</tr>
<tr>
<td>HT use (^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used HT</td>
<td>53</td>
<td>90,396</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Ever used HT</td>
<td>74</td>
<td>126,153</td>
<td>0.98</td>
<td>0.71–1.37</td>
</tr>
</tbody>
</table>

**HT**, menopausal hormone therapy; **ET**, estrogen therapy; **EPT**, estrogen and progestin therapy; **ET/unknown PT**, estrogen therapy with unknown progestin therapy. Unknown oral contraceptive use accounted for 1 cancer and 1,551 person-years; RR = 1.80 (95% CI, 0.25–12.94). Unknown duration of estrogen therapy use accounted for 5 cancers and 10410 person-years; RR = 0.78 (95% CI, 0.31–1.97).

\(^1\)Adjusted for age, calendar year and smoking status (never, former or current). Further adjustment for combined smoking status and duration did not change the results (see Material and Methods).–2Among post menopausal women only. Among post menopausal women women who used ET only; excludes women whose duration of use was unknown.

\(^2\)Adjusted for age, calendar year and smoking status (never, former or current). Further adjustment for combined smoking status and duration did not change the results (see Material and Methods).–2Among post menopausal women only.
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 pop-
ulation-based cohort of Olsson et al.25 showed bladder cancer risk
among smokers was decreased for those who ever used HT com-
pared 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 in-
creased 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
HT7,18 in BCDDP are consistent with the small increased relative
risks noted in other studies, which argues against significant HT ex-
posure misclassification. Other studies have shown that self-reported
oral contraceptive use and recall of self-reported reproductive fac-
tors, 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 dif-
fferences 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 can-
cer risk between men and women are needed.

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