Environmental Tobacco Smoke and Bladder Cancer Risk in Never Smokers of Los Angeles County

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Abstract

Cigarette smoking is a major risk factor for bladder cancer and a prominent point source of 4-aminobiphenyl (4-ABP), a recognized human bladder carcinogen. 4-ABP-hemoglobin (Hb) adducts are established biomarkers of 4-ABP exposure in humans. The role of environmental tobacco smoke (ETS) in the etiology of bladder cancer is largely unknown. As part of a large population-based bladder cancer study in Los Angeles County, lifetime exposure to ETS was ascertained for 148 cases and 292 control subjects who had never used any tobacco products over their lifetime. 4-ABP-Hb adducts were quantitatively measured on 230 control subjects. Female lifelong nonsmokers living with two or more smokers during childhood were significantly related to risk of bladder cancer [odds ratio (OR), 3.08; 95% confidence interval (95% CI), 1.16–8.22]. During adulthood, 2-fold risks were seen among women living with a spouse/domestic partner who smoked for ≥10 years or having a coworker who smoked in an indoor environment for ≥10 years. When all sources of ETS exposure were combined, a statistically significant, dose-dependent association (P for trend = 0.03) was noted in women, with the OR for the highest category of ETS exposure being 5.48 (95% CI, 1.06–28.36). Levels of 4-ABP-Hb adducts varied by ETS exposure status among female control subjects. Mean level was lowest in women never exposed to ETS (16.4 pg/g Hb) and highest in those with current ETS exposure (23.6 pg/g Hb). ETS exposure was associated with neither bladder cancer risk nor 4-ABP-Hb adduct levels in male lifelong nonsmokers. In conclusion, ETS is a risk factor for bladder cancer in women who were lifelong nonusers of any tobacco products. [Cancer Res 2007;67(15):7540–5]

Introduction

Bladder cancer is the fourth most common cancer among males and the ninth most common cancer among females in the United States (1). There were ~63,210 incident cases of bladder cancer and ~13,180 deaths due to bladder cancer in 2005 (1). Cigarette smoking is believed to be the most important risk factor for bladder cancer in the United States, accounting for ~50% of all cases (2). 4-Aminobiphenyl (4-ABP) is an established human bladder carcinogen, capable of forming DNA adducts and inducing mutations in DNA. Cigarette smoking is recognized as the most prominent point source of 4-ABP exposure in humans. 4-ABP-hemoglobin (Hb) adduct levels correlate well with total DNA adduct levels in exfoliated urothelial cells (3) and, therefore, are viewed as valid biomarkers of 4-ABP exposure to the human bladder (4).

In the 1999 Massachusetts Benchmark Study, 4-ABP was found to be 5.4 times more concentrated in sidestream (20.8–31.8 ng/cigarette) than mainstream tobacco smoke (1.8–7.8 ng/cigarette; ref. 5). Animal studies have shown that environmental tobacco smoke (ETS) can induce DNA adducts in bladder cells (6, 7). In humans, exposure to ETS increases 4-ABP-Hb adduct levels (4, 8–10) and urinary mutagenicity in nonsmokers (11), suggesting that ETS exposure may play a role in the development of bladder cancer among never smokers. The U.S. Environmental Protection Agency has concluded that ETS is a human lung carcinogen (12). The 2006 Surgeon General’s report also has concluded that there is sufficient evidence for a causal role of ETS in lung cancer among lifelong nonsmokers. The role of ETS in the development of bladder cancer is less certain. Thus far, five studies have examined the role of ETS in relation to bladder cancer among lifelong nonsmokers (13–17) and results are inconclusive.

As part of the Los Angeles Bladder Cancer Study, a population-based case-control study of bladder cancer in Los Angeles County, California, we collected lifetime domestic and occupational ETS exposure information from bladder cancer patients and healthy control subjects who were lifelong nonsmokers. This report describes our findings on the ETS-bladder cancer association and the variation in 4-ABP-Hb adduct levels by ETS exposure status among control subjects.

Materials and Methods

Study subjects. From 1987 to 1999, we conducted a population-based case-control study of bladder cancer in Los Angeles County via in-person interviews (18). Cases were non-Asians ages 25 to 64 years, with histologically confirmed bladder cancer diagnosed between January 1987 and April 1996. Cases were identified through the Los Angeles County Cancer Surveillance Program, the largest of the Surveillance, Epidemiology and End Results cancer registries (19). In total, 2,384 incident bladder cancer cases were identified. Two hundred and ten (9%) died before we could contact them or were too ill to be interviewed. Permissions to contact 99 (4%) patients were refused by their physicians. Four hundred and four patients (17%) refused to participate in the study. We interviewed 1,671 (70%) bladder cancer patients.

For each case, we chose one control who was individually matched to the index case by gender, date of birth (±5 years), race (non-Hispanic White, Hispanic White, or African-American), and neighborhood of residence at the time of cancer diagnosis of the index cases (18). The control subjects were identified by a standard procedure defining a sequence of houses on specified neighborhood blocks (18). For the 1,671 interviewed patients, 1,586 eligible control subjects were identified and interviewed. Among them, 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-order eligible controls. All study subjects signed informed consent forms, approved by the Human Subjects Committee at the University of Southern California Keck School of Medicine.

**Data collection.** A structured questionnaire was used during interview to request general and exposure information up to 2 years before diagnosis of cancer for the cases and 2 years before diagnosis of cancer of the index case for the matched controls. Each subject was asked to report information on demographic characteristics, lifetime use of tobacco products and alcohol, usual adult dietary habits, lifetime occupational history, prior medical conditions, and prior use of medications.

Starting from January 1992, all cases and their matched controls were asked to donate blood and urine samples at the end of the in-person interview. Nonsmokers at the time of interview or blood draw were asked to complete a supplemental questionnaire soliciting lifetime history of ETS exposure. Questions on ETS exposure included the following four settings: (a) smoking history (ever/never, duration of smoking cigarettes, cigars or pipe at home while living with the subject) of parents and other household members during subject’s childhood (i.e., before 18 years of age); (b) smoking history (ever/never, intensity and duration by type of tobacco product used at home and while living with the subject) of each spouse/domestic partner or other household members during subject’s adulthood (i.e., after 18 years of age); (c) lifetime ETS exposure on the job (hours per day spent in an indoor environment during which a coworker was smoking and duration of this exposure); and (d) ETS exposure for at least 2 h per week on a regular basis in social settings (hours per week spent in an area filled with cigarette smoke and duration of this exposure) by each decade of life from ages 20 to 60 years.

We obtained ETS exposure information on 148 (89.7%) of the 165 bladder cancer patients who had never smoked >100 cigarettes in their lifetime or used cigar, pipe, chewing tobacco, or snuff more than once weekly for ≥6 months. Similarly, we obtained ETS information on 292 (96.4%) of the 303 control subjects who were lifelong nonusers of any tobacco products. For ETS exposure during childhood (up to 18 years of age), a score of 0 was assigned to subjects without any household members who smoked cigarettes or other tobacco products, a score of 1 to those with one or an unknown number of household member who smoked at home, and a score of 2 to those with two or more household members who smoked at home. Similarly, we assigned scores of 0, 1, or 2 to subjects with no, <10 years (including unknown number of years), and ≥10 years of exposure to ETS from domestic, occupational, and social settings, respectively, during adulthood. Ten cases and 13 controls had unknown occupational ETS exposure status and their occupational score was assigned a value of 0. We then created an index of lifetime ETS exposure by summing the assigned score (range, 0–2) for each setting over the four explicitly asked settings (childhood, adulthood/domestic, adulthood/workplace, and adulthood/social). This lifetime exposure index has a maximum value of 8 and a minimum value of 0.

**Laboratory tests.** Plasma, buffy coat, and RBCs were isolated from heparinized whole blood and serum from unheparinized whole blood. All blood components were stored at −80°C before analysis. RBCs were sent on dry ice to the Massachusetts Institute of Technology for quantitative analysis of 4-ABP-Hb adducts as described previously (20). Samples were identifiable only by code numbers so that laboratory personnel had no knowledge or the case/control status of the test samples. Index cases and their individually matched controls were always tested in a single laboratory batch. For cases without matched controls or controls without matched cases, the number of cases was comparable with the number of controls in any given laboratory batch (21).

**Statistical analysis.** Unconditional logistic regression models were used to estimate the odds ratios (OR), their 95% confidence intervals (95% CI), and corresponding P values. We broke the original matched pairs of cases and controls to maximize the sample size for the present analysis. In other words, never smoking cases were included in this analysis, although their individually matched control subjects were excluded from the analysis due to their history of smoking and, conversely, for never smoking control subjects. The matching factors age, gender, and race/ethnicity were included as covariates. We first fitted logistic regression models with the following covariates: age, gender, race/ethnicity (non-Hispanic White, Hispanic White, African-American), and level of education (high school graduate or below, 1-3 years of college, college graduate). We then repeated the analysis with additional covariates, which were found to be risk factors for bladder cancer in the Los Angeles Bladder Cancer Study (22-24). These included lifetime use of nonsteroidal anti-inflammatory drugs (never use, <1,441 pills, ≥1,441 pills over lifetime), carotenoid intake (quintiles), ever use of permanent hair dyes (yes, no), and history of high-risk jobs (yes, no). Results were similar with or without adjustment for this second set of potential confounders. Therefore, results presented in the article were derived from models with only age, gender, race/ethnicity, and level of education as covariates.

We also examined current, past, and never exposure to ETS in relation to levels of 4-ABP-Hb adducts. Among the 292 control subjects, 59 had no 4-ABP-Hb adduct measurements and 3 other subjects reported using cigars or snuff during the preceding 60 days of blood draw, which could have effect on the levels of 4-ABP-Hb adducts in blood. Therefore, these 62 control subjects were excluded from the analysis for the association between ETS exposure and 4-ABP-Hb adduct levels.

It is known that 4-ABP-Hb adducts largely reflect the host’s exposure status during the preceding 3 months (25). Therefore, we defined current exposure to ETS as any exposure to ETS during the 3 months preceding blood draw. Among the 230 control subjects with available 4-ABP-Hb adduct measurements, information on ETS exposure during the 3 months before blood draw was unavailable for 87 subjects. Thus, their last known ETS exposure status was used to determine their status for ETS exposure at blood draw. For these 87 subjects, the mean time interval between the last known ETS exposure status and blood draw was 4.0 years (range, 1–10 years). We analyzed the data with and without inclusion of these 87 subjects, and the two sets of results were similar. Thus, results presented were derived from the total data (n = 230).

The distribution of 4-ABP-Hb adducts was markedly skewed; therefore, their values were logarithmically transformed before statistical analysis. Geometric (as opposed to arithmetic) mean values of 4-ABP-Hb adducts were presented. The analysis of covariance method was used to compare Hb adduct levels across varying levels of ETS exposure. We also used the unconditional logistic regression method to examine the association between ETS exposure and 4-ABP-Hb adduct levels.

**Table 1. Demographic characteristics of never smokers, the Los Angeles Bladder Cancer Study, 1987 to 1999**

<table>
<thead>
<tr>
<th>Age, y (%)*</th>
<th>Cases</th>
<th>Controls</th>
<th>Two-sided P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>19</td>
<td>13</td>
<td>0.52</td>
</tr>
<tr>
<td>45–49</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>55–59</td>
<td>22</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>33</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53.4 (9.1)</td>
<td>54.4 (8.8)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Age at cancer diagnosis for cases and at the time of cancer diagnosis of the index cases for controls.
between ETS status and risk of having high levels of 4-ABP-Hb adducts. The sex-specific median values (19.35 pg/g Hb for men and 20.70 pg/g Hb for women) were used to classify subjects into high (greater than median value) or low levels of 4-ABP.

We used the formula

\[
P_k^{\text{i}} = \frac{\sum_{i} P_i \cdot (\text{OR}_i - 1)}{1 + \sum_{i} P_i \cdot (\text{OR}_i - 1)}
\]

described in Rockhill et al. (26) to calculate the population attributable risk fraction. This formula allows for the use of more than two levels of the exposure under study in the estimation of the population attributable risk.

Statistical analyses were done using the Statistical Analysis System version 9.1 (SAS Institute, Inc.) statistical software package. All \( P \) values are two sided. \( P < 0.05 \) was considered statistically significant.

**Results**

The mean age (±SD) of bladder cancer patients at cancer diagnosis was 53.4 (±9.1) years, whereas the mean age of the controls at the time of cancer diagnosis of the index cases was 54.4 (±8.8) years. The distributions by gender, race/ethnicity, and level of education were similar between cases and controls (Table 1).

**ETS and bladder cancer risk.** Sixty-one percent of bladder cancer cases and 63% of control subjects reported exposure to ETS at home during childhood. During adulthood, 44% of cases and 49% of controls were exposed to ETS at home, 61% of cases and 62% of controls were exposed at work, and 29% of cases and 28% of controls were exposed under social settings. Among men, ETS exposure regardless of time period (childhood or adulthood) or circumstance (at home, at work, or socially) was unrelated to bladder cancer risk in lifelong nonsmokers. In contrast, there was a consistent positive association between ETS exposure and bladder cancer risk in lifelong nonsmoking women (Table 2). Living with two or more smokers during childhood conferred a statistically significant 3-fold increased risk (OR, 3.08; 95% CI, 1.16–8.22). On the other hand, among childhood ETS-positive subjects, the duration of such exposure was unrelated to risk of bladder cancer.

### Table 2. Bladder cancer risk in relation to ETS exposure among never smokers, the Los Angeles Bladder Cancer Study, 1987 to 1999

<table>
<thead>
<tr>
<th>ETS exposure</th>
<th>All subjects</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case/control</td>
<td>OR</td>
<td>Case/control</td>
</tr>
<tr>
<td>Childhood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57/107</td>
<td>1.00</td>
<td>46/73</td>
</tr>
<tr>
<td>Yes</td>
<td>90/185</td>
<td>0.91</td>
<td>60/127</td>
</tr>
<tr>
<td>1 smoker</td>
<td>50/107</td>
<td>0.88</td>
<td>38/69</td>
</tr>
<tr>
<td>&gt;1 smoker</td>
<td>40/77</td>
<td>0.97</td>
<td>22/38</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td>0.85</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Domestic setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>83/150</td>
<td>1.00</td>
<td>70/117</td>
</tr>
<tr>
<td>Yes</td>
<td>65/142</td>
<td>0.85</td>
<td>36/83</td>
</tr>
<tr>
<td>&lt;10 y</td>
<td>42/86</td>
<td>0.88</td>
<td>31/58</td>
</tr>
<tr>
<td>≥10 y</td>
<td>22/51</td>
<td>0.82</td>
<td>5/24</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td>0.47</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Occupational setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>54/106</td>
<td>1.00</td>
<td>38/67</td>
</tr>
<tr>
<td>Yes</td>
<td>84/173</td>
<td>0.98</td>
<td>60/123</td>
</tr>
<tr>
<td>&lt;10 y</td>
<td>33/71</td>
<td>0.93</td>
<td>23/43</td>
</tr>
<tr>
<td>≥10 y</td>
<td>44/90</td>
<td>0.98</td>
<td>32/70</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td>0.94</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Social setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>105/210</td>
<td>1.00</td>
<td>74/145</td>
</tr>
<tr>
<td>Yes</td>
<td>43/82</td>
<td>1.06</td>
<td>32/55</td>
</tr>
<tr>
<td>&lt;10 y</td>
<td>20/30</td>
<td>1.29</td>
<td>17/20</td>
</tr>
<tr>
<td>≥10 y</td>
<td>23/52</td>
<td>0.92</td>
<td>15/35</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td>0.94</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Cumulative index of ETS exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (low)</td>
<td>14/38</td>
<td>1.00</td>
<td>12/26</td>
</tr>
<tr>
<td>1–3 (intermediate)</td>
<td>85/146</td>
<td>1.61</td>
<td>66/100</td>
</tr>
<tr>
<td>4–8 (high)</td>
<td>49/108</td>
<td>1.28</td>
<td>28/74</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td>0.95</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

*The sum may be less than the total number of subjects due to exclusion of those with unknown status of exposure to ETS within a given setting.

†All ORs were adjusted for age, gender, race/ethnicity, and level of education. ORs in a particular ETS setting were further adjusted for ETS exposure at the other three settings.

‡Two-sided \( P < 0.05 \) for test for \( \text{OR} = 1.0 \).

See Materials and Methods for details.
Very few parents or other household members used tobacco products other than cigarettes. Thus, we could not meaningfully compare the effects of ETS from cigarettes versus other tobacco products on risk of bladder cancer.

In women, living with a spouse/domestic partner who smoked for ≥10 years (OR, 1.97; 95% CI, 0.75–5.16) or having a smoker as a coworker in an indoor environment for ≥10 years (OR, 1.94; 95% CI, 0.72–5.23) both conferred a ~2-fold increased risk. When we summed all sources of ETS exposure into a cumulative score ranging from 0 (no ETS exposure) to 8 (highest ETS exposure), among women, there was a statistically significant, dose-dependent association with risk of bladder cancer (P for trend = 0.03). The OR for the highest category of ETS exposure was 5.48 (95% CI, 1.06–27.9). When women with imputed ETS status were included (five cases of bladder cancer), the OR for the highest category of ETS exposure was 5.51 (95% CI, 1.04–29.14). This is consistent with the gender-specific results on the ETS-bladder cancer association, as women with current ETS exposure had a higher level of risk compared to men who had never used tobacco products.

We computed the population attributable risk fraction for ETS in women using the formula of Rockhill et al. (26) and the values of OR and prevalence in controls given in Table 2. Seventy-four percent of bladder cancer among women who had never used tobacco products could be attributable to ETS.

**Discussion**

The present study shows a dose-dependent relationship between exposure to ETS and risk of bladder cancer among women who were lifelong nonsmokers. The association for ETS exposure during childhood was stronger than that in adulthood, suggesting that children may be more susceptible than adults to the bladder-specific carcinogens in ETS. Our observed results were strongly supported by the findings of a biomarker study reporting that children living with household members, especially the mother, who smoked cigarettes and/or other tobacco products exhibited statistically significantly elevated levels of 4-ABP-Hb relative to children without such exposures (27).

The present study failed to detect a positive ETS-bladder cancer association among men. This gender differential finding is consistent with our earlier observation that female active smokers exhibited a higher level of relative risk for bladder cancer compared to male active smokers of comparable smoking histories (18). These exposure-risk association findings are corroborated by differential Hb adduct levels of 4-ABP, a potent human bladder carcinogen, noted in our female versus male active/passive smoking subjects (18). In the present study, women with current ETS exposure at blood draw were nine times more likely than men to possess elevated Hb adduct level of 4-ABP.

The possible biological mechanism for this gender difference in susceptibility to carcinogens in tobacco smoke is not clear. Previous studies reported a higher expression level of CYP1A1 (which is believed to play a central role in the metabolic activation of 4-ABP) in female smokers compared to male smokers (19). However, the underlying reasons for this difference are not yet fully understood.

### Table 3. 4-ABP-Hb adducts (pg/g Hb) in relation to ETS exposure status at blood draw among control subjects who were lifelong nonsmokers, the Los Angeles Bladder Cancer Study, 1987 to 1999

<table>
<thead>
<tr>
<th>ETS exposure</th>
<th>All subjects</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>4-ABP-Hb (95% CI)*</td>
<td>n</td>
</tr>
<tr>
<td>Never</td>
<td>27</td>
<td>19.3 (15.1–24.6)</td>
<td>19</td>
</tr>
<tr>
<td>Formerly exposed</td>
<td>147</td>
<td>23.1 (20.1–26.5)</td>
<td>103</td>
</tr>
<tr>
<td>Currently exposed</td>
<td>56</td>
<td>22.3 (18.6–26.7)</td>
<td>38</td>
</tr>
</tbody>
</table>

*p values for trend.*

**4-ABP-Hb adducts (pg/g Hb)**

<table>
<thead>
<tr>
<th>ETS exposure</th>
<th>Low/High OR (95% CI)*</th>
<th>Low/High* OR (95% CI)*</th>
<th>Low/High* OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>16/11 1.00</td>
<td>10/9 1.00</td>
<td>6/2 1.00</td>
</tr>
<tr>
<td>Formerly exposed</td>
<td>72/75 1.58 (0.67–3.72)</td>
<td>50/53 1.14 (0.42–3.11)</td>
<td>22/22 5.84 (0.89–38.32)</td>
</tr>
<tr>
<td>Currently exposed</td>
<td>27/29 1.78 (0.67–4.67)</td>
<td>20/18 1.00 (0.32–3.15)</td>
<td>7/11 9.22 (1.22–69.40)</td>
</tr>
</tbody>
</table>

*p values for trend.*

**Geometric mean and 95% CI.**
of tobacco carcinogens) and higher levels of DNA adducts in the normal lung tissues of female smokers than male smokers (28), suggesting that genetic factor(s) may play a role in this gender difference in susceptibility to tobacco-related cancers. However, in our Los Angeles Bladder Cancer Study, genotype/phenotype frequencies of glutathione S-transferase M1 and N-acetyltransferase 2 (29), two genetic factors related to bladder cancer risk (30, 31), were comparable between male and female subjects. Further studies are warranted to explore intrinsic and/or environmental factors contributing to this gender difference in risk of bladder cancer associated with exposure to tobacco carcinogens.

Risk of bladder cancer from ETS exposure was previously evaluated in several epidemiologic studies. The early studies generally found a null association between exposure to ETS and risk of bladder cancer (13–16), largely due to the small sample size and suboptimal measurements in ETS exposure. A recent study reported a 3-fold increase in risk of bladder cancer among women who never smoked cigarettes but had high occupational ETS exposure (P for trend = 0.03). The same study did not find an ETS-bladder cancer association among men (17). These results are consistent with our findings in the present study. A stronger association for bladder cancer risk with occupational than domestic ETS exposure may be explained by the more intense and sustained ETS exposure under the former circumstance (32–34) and is consistent with previous results on ETS and lung cancer (35).

Misclassification of ETS exposure is inevitable (36, 37) because the subject's exposure status was decided retrospectively by recalling other people's smoking habits, and many of the events might be decades old. However, differential misclassification with respect to case/control status is unlikely because ETS exposure has never been known to be a risk factor for bladder cancer. Nondifferential misclassification of the exposure status tends to bias the results toward the null assuming independence of the errors and absence of other biases (38). Thus, underestimation of a true effect rather than creation of a spurious association is more likely to result from misclassification of ETS exposure status in our study subjects.

One strength of the present study is its ability to link levels of 4-ABP-Hb adducts in control subjects to their ETS exposure status. Consistent with our findings that ETS is positively related to bladder cancer in female never smokers, we found that levels of 4-ABP-Hb adducts, a specific biomarker for 4-ABP, an established human bladder carcinogen, are higher in female control subjects positive for ETS exposure than those without such exposure. It is unclear why women formerly exposed to ETS exhibited levels of 4-ABP-Hb adducts intermediate between the high levels in current ETS-exposed women and the low levels in women never exposed to ETS. One possible explanation is that these ETS-positive individuals are more likely than ETS-negative individuals to be currently exposed to other environmental sources of 4-ABP, for example, via industrial processes (39) or the use of commercial hair dyes (40).

Our findings of an increase of 3.6 pg/g Hb of 4-ABP-Hb adducts, on average, between control subjects positive versus negative for ETS are comparable with those of prior studies (8–10, 18). Bartsch et al. (10) noted a mean difference of 6.3 pg/g Hb between nonsmokers with (34.6 pg/g Hb) and without (28.3 pg/g Hb) ETS exposure. In the study conducted by Maclure et al. (9), nonsmokers with detectable levels of cotinine (49.2 pg/g Hb) had a mean level that was 3.3 pg/g Hb higher than those with undetectable levels of cotinine (45.9 pg/g Hb). The magnitude of these ETS-related differences in 4-ABP-Hb is considerably smaller than comparable differences between active cigarette smokers and nonsmokers. In the Los Angeles Bladder Cancer study, men who smoked up to one pack of cigarettes per day showed an increase of 23 pg/g Hb relative to nonsmokers (18).

Earlier, we had reported that lifelong nonsmoking cases exhibited statistically significantly higher levels of 4-ABP than lifelong nonsmoking controls (26.1 versus 21.4 pg/g; P = 0.002; ref. 21). Furthermore, this statistically significant difference remained after adjustment for ETS exposure and use of permanent hair dyes. Therefore, our results suggest that, although ETS exposure may be one risk factor for bladder cancer in nonsmokers, there exist other, as-yet-unidentified environmental sources of 4-ABP relevant to bladder cancer development.

In summary, the present study shows a statistically significant positive association between ETS exposure and bladder cancer risk in female lifelong nonsmokers. This positive ETS-bladder cancer association was supported by elevated 4-ABP-Hb adducts in ETS-positive women (4-ABP is an established human bladder carcinogen). If the ETS-bladder cancer association in women is causal, ~70% of bladder cancer among female lifelong nonsmokers could be attributed to exposure to ETS. The present study provides the strongest evidence thus far in support of ETS as a risk factor for bladder cancer in female lifelong nonsmokers.

Acknowledgments


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References

Announcements

MEETING OF THE RADIATION RESEARCH SOCIETY

The annual meeting of the Radiation Research Society will be held at the State University of Iowa, Iowa City, on June 22–24, 1953. The Society will be the guest of the University, and all meetings will be held on the campus. The program will consist of: (1) Two symposia, one on "The Effects of Radiation on Aqueous Solutions," which includes the following speakers: E. S. G. Barron, Edwin J. Hart, Warren Garrison, J. L. Magee, and A. O. Allen. The second is "Physical Measurements for Radiobiology" and companion talks by Ugo Fano, Burton J. Moyer, G. Failla, L. D. Marinelli, and Payne S. Harris. (2) On Monday night, June 22, a lecture by Dr. L. W. Alvarez on meson physics has been tentatively scheduled. On Tuesday night, June 23, Dr. L. H. Gray of the Hammersmith Hospital, London, will speak on a topic to be announced. Dr. Gray's lecture is sponsored by the Iowa Branch of the American Cancer Society. Those desiring to report original research in radiation effects, or interested in attending or desiring additional information, please contact the Secretary of the Society, Dr. A. Edelmann, Biology Department, Brookhaven National Laboratory, Upton, L.I., New York.

ERRATUM

The following correction should be made in the article by Beck and Valentine, "The Aerobic Carbohydrate Metabolism of Leukocytes in Health and Leukemia. I. Glycolysis and Respiration," November, 1952, page 891; substitute for the last paragraph:

The data in Table S permit several interesting calculations. If one compares the amount of glucose actually disappearing with the sum of the amount equivalent to lactic acid produced plus that equivalent to O₂ consumption, it is seen that the amount of glucose "cleavage products" exceeds the amount of glucose utilized by 12 per cent in N and 27 per cent in CML and is exceeded by the glucose utilized by 16 per cent in CLL. If the assumption is made that, in this respect, the myeloid and lymphoid cells of leukemia are similar to those of normal blood, it may be that the computed normal figure represents a summation of the myeloid (M) and lymphoid (L) cells that make up the normal leukocyte population. Thus, if M = +0.27 and L = —0.16 and the normal differential is 65 per cent M and 35 per cent L, then

$$0.65 (+0.27) + 0.35 (-0.16) = +0.12$$

a figure identical to the observed +0.12 for normal leukocytes.
Environmental Tobacco Smoke and Bladder Cancer Risk in Never Smokers of Los Angeles County

Xuejuan Jiang, Jian-Min Yuan, Paul L. Skipper, et al.


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