Gender- and Smoking-Related Bladder Cancer Risk

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Background: **There is growing evidence that, when smoking habits are comparable, women incur a higher risk of lung cancer than men. Because smokers are also at risk for bladder cancer, we investigated possible sex differences in the susceptibility to bladder cancer among smokers.** ***Methods:*** **A population-based, case–control study was conducted in Los Angeles, CA, involving 1514 case patients with bladder cancer and 1514 individually matched population control subjects. Information on tobacco use was collected through in-person interviews. Peripheral blood was collected from study participants to measure 3- and 4-aminobiphenyl (ABP)–hemoglobin adducts, a marker of arylamine exposure. Data were analyzed to determine whether the risk of bladder cancer differs between male and female smokers and whether female smokers exhibit higher levels of ABP–hemoglobin adducts than male smokers with comparable smoking habits. All statistical tests were two-sided.** ***Results:*** **Cigarette smokers had a statistically significant 2.5-fold higher risk (95% confidence interval = 2.1 to 3.0) of bladder cancer than never smokers. Use of filtered versus nonfiltered cigarettes, low-tar versus higher tar cigarettes, or the pattern of inhalation did not modify the risk. The risk of bladder cancer in women who smoked was statistically significantly higher than that in men who smoked comparable numbers of cigarettes (*P* = .016 for sex–lifetime smoking interaction). Consistent with the sex difference in smoking-related bladder cancer risk, the slopes of the linear regression lines of the 3- and 4-ABP–hemoglobin adducts by cigarettes per day were statistically significantly steeper in women than in men (*P* values for sex differences <.001 and .006, respectively).** ***Conclusion:*** **The risk of bladder cancer may be higher in women than in men who smoked comparable amounts of cigarettes. [J Natl Cancer Inst 2001;93: 538–45]**

In the United States, each year an estimated 51 200 cases of bladder cancer are diagnosed and more than 10 600 people die of the disease *(1).* In fact, bladder cancer makes up approximately 6% of all new cancer cases diagnosed in men and 2% of those diagnosed in women. The most established etiologic risk factors for bladder cancer are cigarette smoking and occupational exposure to arylamines *(2).* Studies [reviewed in *(2)*] have consistently shown a twofold to threefold increased risk for bladder cancer in cigarette smokers compared with nonsmokers. However, data are sparse regarding the possible influence of cigarette composition (filtered versus nonfiltered, low-tar versus higher tar) on the risk of bladder cancer *(2).*

There is growing evidence that, when smoking habits are comparable, women incur a higher risk for lung cancer than men *(3–5).* At present, there is little information on possible sex differences in the risk of smoking-related bladder cancer. In this study, which involved more than 1500 case patients with bladder cancer and an equal number of population control subjects in Los Angeles, CA, we examined various parameters of cigarette smoking in relation to bladder cancer risk, including a comparison of the risk in male versus female smokers, the risk associated with use of filtered versus nonfiltered cigarettes and low-tar versus higher tar cigarettes, and the risk associated with varying patterns of smoking inhalation.

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See "Notes" following "References."

Subjects and Methods

Subjects

The Los Angeles County Cancer Surveillance Program *(6),* the population-based Surveillance, Epidemiology, and End Results (SEER)[1] cancer registry of Los Angeles County, identified 2098 non-Asian patients, aged 25–64 years, with histologically confirmed bladder cancer diagnosed between January 1, 1987, and April 30, 1996. Among these patients, 175 died before we could contact them or were too ill to be interviewed, 267 refused to be interviewed, and 74 were not contacted because their physicians failed to give their permission. Thus, we interviewed 1582 (75%) of 2098 of all eligible patients.

For each interviewed case patient, we sought to recruit a control subject who was matched to the index case patient by sex, date of birth (within 5 years), race (non-Hispanic white, Hispanic, or African-American), and neighborhood of residence at the time of cancer diagnosis. To search for these neighborhood control subjects, we followed an invariant procedure that defines a sequence of houses on specified neighborhood blocks. We attempted to identify the sex, age, and race of all inhabitants of each housing unit; not at home units were systematically revisited to complete the census. The first resident along this defined route who satisfies all eligibility criteria for a control subject is asked to participate in this study (i.e., first eligible control subject). If the individual refuses, the next eligible control subject (i.e., second eligible control subject) in the sequence is asked and so on (i.e., third eligible control subject), until we locate an eligible control subject who agrees to be interviewed. When we failed to find any resident who met our matching criteria after canvassing 150 housing units, we excluded race from the matching criteria. If a matched control subject based on this relaxed criterion could not be found within a maximum of 300 housing units, the case patient was dropped from the study. Sixty-eight case patients were dropped from the study because of lack of matched control subjects, and 20 control subjects were not matched by race to index case patients. Of the matched 1514 control subjects interviewed, 1049 (69%) were the first eligible control subjects, and 307 (20%) and 158 (10%) were the second and third eligible control subjects, respectively. All of the study subjects signed informed consent forms (separate forms for interview and blood donation) approved by the University of Southern California Human Subjects Committee.

Data Collection

In-person structured interviews were conducted in each subject's home. The questionnaire requested information up to 2 years before the diagnosis of bladder cancer for case patients or 2 years before the diagnosis of cancer of the index case patient for the matched control subject. Information was requested on demographic characteristics, such as height and weight, lifetime use of tobacco products and alcohol, usual adult dietary habits, lifetime occupational history, prior medical conditions, and prior use of medications. All interviews were conducted by the same team of interviewers throughout the data collection; most case patients and control subjects in a given case–control pair were interviewed by the same interviewer. Among case patients, the median time interval between bladder cancer diagnosis and interview was 11 months, and 80% were interviewed within 18 months of diagnosis.

To gather information on cigarette use, the subject was asked whether he/she had ever smoked at least one cigarette a day for 6 months or longer. If the answer was "yes," the subject was classified as an "ever cigarette smoker." We then asked questions about the age at which the subject started to smoke on a daily basis, smoking status (continuing or quitting smoking) 2 years before the cancer diagnosis of the index case patient, duration (number of years) of regular smoking, and average number of cigarettes smoked per day. We also asked questions regarding the usual type of cigarettes smoked (filtered only, nonfiltered only, or both types equally) and the usual pattern of inhalation (deep, moderate, or light). If the answer was "no," the subject was classified as a "never cigarette smoker."

Beginning in January 1992, we asked 897 bladder cancer case patients and their matched control subjects for the brand names of the usual cigarettes smoked and asked for the length of time that each type of cigarette (filtered, nonfiltered, and low tar) was smoked. With the use of a database that gives the chemical composition of each brand-name cigarette manufactured in the United States, lifetime exposure to tar from cigarettes was computed for 1794 study subjects *(7).*

Each subject was also asked if he/she had ever used cigars, pipes, chewing tobacco, or snuff at least once a week for 6 months or longer. From those who answered 'yes' to any of these tobacco products, we obtained their age at first regular use, the number of years of regular use, and the average amount of tobacco used per week.

Blood Sample Collection and 3- and 4-Aminobiphenyl–Hemoglobin Adduct Measurements

Beginning in January 1992, all case patients and their matched control subjects were asked for a blood sample donation at the end of the in-person interviews. We obtained a blood sample from 658 (73%) of 897 case patients and from 705 (79%) of 897 control subjects. Two 10-mL tubes of heparinized whole blood were collected from each study subject. Plasma, buffy coat cells, and red blood cells were isolated, washed, and stored at –80 °C until analysis. Serum was isolated from an additional 10 mL of unheparinized whole blood and stored at –80 °C until analysis. Samples were sent on dry ice to S. R. Tannenbaum at the Massachusetts Institute of Technology, Cambridge, MA, where investigators were blinded to the samples (which were identified only by their code numbers) and analyzed them for 3- and 4-aminobiphenyl (ABP)–hemoglobin adducts as described previously *(8,9).* Of those subjects who donated blood, 3- and 4-ABP–hemoglobin adduct values were determined in 641 (97%) case patients and in 684 (97%) control subjects. Tobacco smoke contains small quantities of 3- and 4-ABPs, which are considered to be putative tobacco carcinogens responsible for bladder cancer development in smokers *(2).* 3- and 4-ABP–hemoglobin adducts are recognized as valid biomarkers of the internal dose of ABPs to the target organ, i.e., bladder, and their levels essentially reflect exposure during the 60 days before blood collection *(2).* Because tobacco use is the major source of ABP exposure in the United States *(2),* all subjects who donated blood were further asked detailed questions about their use of tobacco products for the 2 months before the blood was drawn.

Statistical Analysis

Data were first analyzed by standard matched-pair methods, including conditional logistic regression methods *(10).* The associations of bladder cancer with various exposure indices of tobacco use were measured by odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). When the case patient or the control subject of a pair failed to answer the relevant questions, we eliminated that case–control pair from the corresponding analysis. We restricted the analysis of the potential effects of cigarette composition and inhalation pattern on bladder cancer risk to "ever cigarette smokers." We broke the case–control matching in these analyses to maximize the number of case patients and control subjects included and used unconditional logistic regression methods *(10).* Ten age–sex strata (age groups of <46, 46–50, 51–55, 56–60, and ≥60 years for each sex) were included in the unconditional models to adjust for age and sex.

We repeated the above-described analyses with and without adjustment for other independent risk factors for bladder cancer, including use of nonsteroidal anti-inflammatory drugs *(11),* high-risk occupations (truck/bus/taxi driver, aluminum product worker, and hairdresser) *(12),* and dietary carotenoids (unpublished data). There were no material changes in the results with or without adjustment for these potential confounders. Data presented in this report are derived from analyses without adjustment for these potential confounders.

We also examined the possibility that men and women who smoked comparable amounts of cigarettes might exhibit varying levels of 3- and 4-ABP–hemoglobin adducts. To test this hypothesis, we used the analysis of covariance method to compare the slopes of the linear regression lines between 3- and 4-ABP–hemoglobin adducts and the number of cigarettes smoked per day in male versus female subjects *(13).* Results are presented for control subjects only (538 males and 146 females) and for case patients and control subjects combined (1039 males and 285 females). The inclusion of bladder cancer case patients in the covariance analysis was justified because we found no difference in the slopes of the 3- and 4-ABP–hemoglobin adducts–cigarettes/day regression lines between case patients and control subjects in both men and women. The distributions of 3- and 4-ABP–hemoglobin adducts in our study population were markedly skewed; thus, before analysis, all adduct values were logarithmically transformed. All *P* values were two-sided.

Results

To determine whether, among smokers, sex differences affect their risk of bladder cancer, we conducted a population-based, case–control study. In our study, the mean age of the case patients at diagnosis of bladder cancer was 56.2 ± 7.7 years; the mean age of the control sub-

jects was 56.4 ± 8.3 years. The study included 2826 non-Hispanic whites (1413 case patients and 1413 control subjects), 123 Hispanics (58 case patients and 65 control subjects), 78 African-Americans (42 case patients and 36 control subjects), and one Native American case patient.

Tobacco Use and Risk of Bladder Cancer

We first assessed the risk of bladder cancer in the 1276 (1017 men and 259 women) case patients and in the 1053 (868 men and 185 women) control subjects who regularly used any type of tobacco products (cigarettes, cigars, pipe, or chewing tobacco/snuff). Compared with lifelong nonusers, regular users of any tobacco product had an increased risk of bladder cancer (OR = 2.4; 95% CI = 2.0 to 2.8). The increased risk was confined to those who smoked cigarettes (OR = 2.5; 95% CI = 2.1 to 3.0). Subjects who used only noncigarette products did not have an increased risk of bladder cancer (36 case patients and 81 control subjects; OR = 0.9 [95% CI = 0.6 to 1.3]). Similarly, no associations were found between bladder cancer risk and cigar (11 case patients and 20 control subjects; OR = 1.0 [95% CI = 0.4 to 2.2]), pipe (13 case patients and 28 control subjects [OR = 0.9; 95% CI = 0.5 to 1.8]), or chewing tobacco/snuff (one case patient and six control subjects; OR = 0.4 [95% CI = 0.05 to 3.3]) users who did not smoke cigarettes. Likewise, no association was found between bladder cancer risk and users of two or more types of noncigarette tobacco products (11 case patients and 27 control subjects; OR = 0.8 [95% CI = 0.4 to 1.6]).

We next assessed the association between the risk of bladder cancer and the behavior characteristics of cigarette smoking. Table 1 presents the relationships between the intensity of cigarette smoking (i.e., the number of cigarettes smoked per day), the duration of cigarette smoking (i.e., the number of years that the subject has smoked), smoking cessation (i.e., the number of years since the subject last smoked), and the risk of bladder cancer analyzed separately for men and women and for both sexes combined. For both sexes, there was a general increase in the risk of bladder cancer associated with an increase in the number of cigarettes smoked per day and an increase in the number of years of regular smoking (both P values for trend were <.001). Ex-smokers reduced their risk of bladder cancer when they quit smoking. The decrease in risk was proportional to the length of time since they quit smoking (Table 1).

We next assessed whether there were associations between the risk of bladder cancer and smoking various types of cigarettes or between risk and patterns of inhalation. Use of filtered versus nonfiltered cigarettes did not reduce the smoking-related risk of bladder cancer (Table 2). There was no statistically significant difference between ORs for subjects who mainly smoked filtered cigarettes and those who mainly smoked nonfiltered cigarettes. Among subjects with comparable intensity and duration of cigarette

Table 1. Cigarette smoking and risk of bladder cancer*

	Total			Men			Women		
	No. of case patients	No. of control subjects	OR† (95% CI)	No. of case patients	No. of control subjects	OR† (95% CI)	No. of case patients	No. of control subjects	OR† (95% CI)
Never smokers	274	542	1.0 (referent)	199	392	1.0 (referent)	75	150	1.0 (referent)
Ever smokers	1240	972	2.5 (2.1 to 3.0)	981	788	2.4 (2.0 to 2.9)	259	184	2.8 (2.0 to 4.0)
Intensity of smoking									
No. of cigarettes smoked/day									
<10	85	122	1.3 (0.96 to 1.8)	44	76	1.2 (0.8 to 1.8)	41	46	1.7 (1.0 to 3.0)
10 to <20	143	178	1.6 (1.2 to 2.1)	96	133	1.4 (1.0 to 2.0)	47	45	2.0 (1.2 to 3.3)
20 to <30	452	367	2.4 (2.0 to 3.0)	350	304	2.2 (1.7 to 2.8)	102	63	3.2 (2.1 to 4.9)
30 to <40	209	124	3.5 (2.6 to 4.6)	182	116	3.1 (2.3 to 4.2)	27	8	6.9 (2.8 to 16.9)
⩾40	349	180	4.2 (3.2 to 5.4)	307	158	4.0 (3.0 to 5.3)	42	22	4.2 (2.2 to 7.7)
P for liner trend			<.001			<.001			<.001
Duration of smoking									
No. of years of smoking									
<10	80	124	1.1 (0.8 to 1.6)	65	96	1.2 (0.8 to 1.7)	15	28	0.8 (0.4 to 1.7)
10 to <20	165	208	1.5 (1.1 to 1.9)	130	167	1.4 (1.1 to 1.9)	35	41	1.5 (0.9 to 2.8)
20 to <30	280	234	2.4 (1.9 to 3.1)	225	188	2.4 (1.8 to 3.2)	55	46	2.3 (1.4 to 3.9)
30 to <40	407	242	3.6 (2.9 to 4.6)	308	198	3.3 (2.5 to 4.3)	99	44	5.4 (3.2 to 9.2)
⩾40	308	164	4.5 (3.4 to 5.8)	253	139	4.2 (3.1 to 5.6)	55	25	6.0 (3.1 to 11.7)
P for linear trend			<.001			<.001			<.001
Smoking cessation									
Ex-smokers	547	610	1.7 (1.4 to 2.1)	458	502	1.7 (1.4 to 2.1)	89	108	1.5 (1.0 to 2.4)
Years since quitting									
<10	217	189	2.3 (1.8 to 2.9)	176	155	2.2 (1.7 to 2.9)	24	38	2.7 (1.5 to 4.8)
10 to <20	185	182	1.9 (1.5 to 2.5)	161	146	2.1 (1.6 to 2.8)	24	36	1.1 (0.6 to 2.1)
⩾20	145	239	1.1 (0.9 to 1.5)	121	201	1.1 (0.8 to 1.5)	41	34	1.1 (0.6 to 2.0)
P for linear trend‡			<.001			<.001			.008
Current smoking	693	362	3.8 (3.1 to 4.7)	523	286	3.6 (2.8 to 4.6)	170	76	4.6 (3.0 to 7.0)

*Similar odds ratios were obtained after adjusting for other risk factors for bladder cancer, including use of nonsteroidal anti-inflammatory drugs, high-risk occupations (truck/bus/taxi driver, aluminum product worker, and hairdresser), and dietary carotenoids. The sum is less than the total number of case patients and control subjects due to the exclusion of subjects with missing values in the analysis.

†OR = odds ratio; CI = confidence interval. Statistical tests were two-sided.

‡The trend test was based on the number of years since quitting smoking (continuous variable) among ex-smokers only.

Table 2. Risk of bladder cancer by cigarette composition and inhalation pattern in ever smokers only

	No. of case patients	No. of control subjects	OR* (95% CI)
Filtered versus nonfiltered			
Usually smoked nonfiltered	431	356	1.0 (referent)
Usually smoked filtered	386	303	1.2 (0.9 to 1.5)
Smoked both types equally	418	309	1.1 (0.9 to 1.4)
Duration of filtered cigarette use, y†,‡			
Nonfiltered only	88	85	1.0 (referent)
1 to <10	74	100	0.9 (0.6 to 1.4)
10 to <20	166	114	1.4 (0.9 to 2.1)
20 to <30	180	138	0.9 (0.6 to 1.4)
⩾30	185	95	1.1 (0.7 to 1.7)
Low-tar versus higher tar†,‡			
Never smoked low tar	486	388	1.0 (referent)
Ever smoked low tar	193	142	0.9 (0.7 to 1.2)
Duration of low-tar cigarette use, y			
Never used low tar	486	388	1.0 (referent)
1 to <10	75	75	0.7 (0.5 to 1.1)
10 to <20	68	36	1.2 (0.8 to 1.9)
⩾20	33	25	0.8 (0.4 to 1.4)
Cumulative tar exposure, g			
<1400	156	176	1.0 (referent)
1400 to <3300	196	174	0.9 (0.6 to 1.2)
⩾3300	320	164	1.0 (0.7 to 1.6)
Inhalation pattern			
Light	166	170	1.0 (referent)
Moderate	668	516	1.2 (0.9 to 1.6)
Deep	386	271	1.1 (0.5 to 1.8)

*OR = odds ratio; CI = confidence interval. Adjusted for age, sex, race, current smoking status (yes or no), number of cigarettes smoked per day, and number of years of smoking. Statistical tests were two-sided.

†Information on duration of filtered cigarette use and use of low-tar cigarettes was requested only from 721 ever-smoking case patients and 550 ever-smoking control subjects interviewed since January 1992 (for details *see* the "Subjects and Methods" section).

‡The sum is less than the total number of case patients and control subjects because of the exclusion of subjects with missing values in the analysis.

smoking, the duration of use of filtered cigarettes or the use of low-tar cigarettes was unrelated to the risk of bladder cancer (Table 2). Cumulative tar exposure from cigarettes showed no appreciable association with the risk of bladder cancer (Table 2). The pattern of inhalation also had no influence on the smoking-related risk of bladder cancer. ORs were comparable among those who inhaled lightly, moderately, or deeply (Table 2). There was no statistical difference in ORs when these exposure–risk associations (filtered versus nonfiltered cigarettes, low-tar versus higher tar cigarettes, or pattern of inhalation) were analyzed in men and women separately and in current and ex-smokers separately. Finally, we also examined tar, filter, and inhalation variables by pack-years (average packs smoked per day × number of years of regular smoking) of smoking (<30 or ⩾30 pack-years). The results were consistently null across strata.

Sex and Risk of Bladder Cancer

We next assessed whether sex-specific effects could be identified. Table 3 shows the effects of smoking intensity and the duration of cigarette smoking on bladder cancer risk analyzed separately for men and women. Men who smoked 40 or more cigarettes per day for 20–39 years had an OR of 4.87 (95% CI = 3.46 to 6.84). For all other smoking categories, the ORs for women were higher than for men (Table 3). For example, in the heaviest smoking category (⩾40 cigarettes smoked per day for ⩾40 years), the OR in women was more than twice that in men (11.49 versus 5.23, respectively). To test for a possible sex difference in smoking-related risk of bladder cancer, we used a product term of sex and the total number of cigarettes smoked over a lifetime (average number of cigarettes smoked per day × 365 days/year × number of years of smoking cigarettes) and included it in a logistic regres-

Table 3. Joint effects of intensity and duration of smoking on risk of bladder cancer by sex*

	No. of years of smoking					
	Men			Women		
No. of cigarettes/day	<20 y	20–39 y	⩾40 y	<20 y	20–39 y	⩾40 y
<20						
No. of case patients/ No. of control subjects†	59/100	65/93	16/16	27/44	48/40	13/7
Odds ratio (CI)‡	1.09 (0.75 to 1.58)	1.52 (1.05 to 2.21)	2.54 (1.14 to 5.68)	0.95 (0.52 to 1.73)	2.65 (1.50 to 4.66)	4.50 (1.63 to 12.42)
20–39						
No. of case patients/ No. of control subjects†	100/128	292/215	140/77	18/20	80/36	31/15
Odds ratio (CI)‡	1.37 (0.99 to 1.90)	2.72 (2.10 to 3.52)	3.77 (2.67 to 5.32)	1.66 (0.76 to 3.60)	4.33 (2.58 to 7.27)	4.98 (2.30 to 10.81)
⩾40						
No. of case patients/ No. of control subjects†	36/35	174/77	97/46	5/5	26/14	11/3
Odds ratio (CI)‡	1.89 (1.12 to 3.18)	4.87 (3.46 to 6.84)	5.23 (3.42 to 8.02)	2.47 (0.65 to 9.43)	4.33 (2.02 to 9.26)	11.49 (2.31 to 57.24)
P value for interaction between lifetime smoking and sex = .016						

*Similar odds ratios were obtained after adjusting for other risk factors for bladder cancer, including use of nonsteroidal anti-inflammatory drugs, high-risk occupations (truck/bus/taxi driver, aluminum product worker, and hairdresser), and dietary carotenoids.

†Number of case patients/control subjects. The sum is less than the total number of case patients and control subjects because of the exclusion of subjects with missing values in the analysis.

‡Odds ratio (95% confidence interval) relative to never-cigarette smokers. Statistical tests were two-sided.

sion model. We found the sex difference to be statistically significant ($P = .016$).

We next determined whether there was a sex difference in the relationship between the levels of 3- and 4-ABP–hemoglobin adducts and the number of cigarettes smoked per day. Table 4 presents the geometric mean levels of 3- and 4-ABP–hemoglobin adducts analyzed by sex and cigarette smoking status for control subjects only and for case patients and control subjects combined. The inclusion of case patients with the control subjects was justified because no difference was noted in the ABP adduct-cigarettes/day linear regressions between case patients and control subjects of the same sex. Table 4 shows that, within each level of smoking, the mean values of 3- and 4-ABP–hemoglobin adducts for women were greater than those for men, even though, on average, they smoked fewer cigarettes per day. We used linear regression analysis to investigate whether possible sex differences could be detected in the proportional increases in 3- and 4-ABP–hemoglobin adducts as a function of the number of cigarettes smoked per day. The differences in the regression slopes between men and women were statistically significant for case patients and control subjects combined, $P<.001$ and $P = .006$, for 3- and 4-ABP–hemoglobin adducts, respectively; for control subjects only, $P = .005$ and $P = .03$, for 3- and 4-ABP–hemoglobin adducts, respectively.

We repeated all analyses after excluding the 20 case–control pairs in which control subjects were not matched by race to the index case patients. The exclusion did not change any of the results described above. We also conducted separate analyses on case–control pairs whose control subjects were the first eligible control subjects (n = 1049) versus the second or third eligible control subjects (n = 465). Similar results were obtained between the two case–control subsets.

Discussion

Consistent with published results *(14–23),* we observed that the duration and intensity of cigarette smoking independently increased the risk of bladder cancer. We confirmed previous reports *(16–19,21–24)* that smoking cessation reduces the risk of bladder cancer and that the effect is proportional to the length of time interval since quitting. We detected a statistically significant difference in the risk of bladder cancer between men and women who smoked. Furthermore, we also demonstrated that, when comparable amounts of cigarettes were smoked, women who smoked had higher levels of 3- and 4-ABP–hemoglobin adducts than men who smoked. This observation is important because arylamines (including ABPs), which are found in cigarette smoke, are believed to play a major role in smoking-induced bladder carcinogenesis *(2).*

Risch et al. *(25)* first raised the provocative question of whether female smokers are at higher risk for lung cancer than male smokers. In their case–control study, they found a statistically significantly higher risk of lung cancer among female smokers than among male smokers. Relative to lifelong nonsmokers, women with 40 pack-years of cumulative smoking had an OR of 27.9 (95% CI = 14.9 to 52.0), almost three times that of men (OR = 9.6; 95% CI = 5.6 to 16.3). Three other studies *(3,26,27)* with sufficient power to address sex differences have reported results consistent with those of Risch et al. *(25).* Women who smoke are at increased risk for all major histologic types of lung cancer *(3,27,28),* although Osann et al. *(27)* found a sex difference only for small-cell lung carcinoma. One possible explanation for the observed sex difference is that sex hormones play some role in lung cancer development, an hypothesis with limited epidemiologic support *(28–30).*

Laboratory studies *(4,5,31)* have provided possible additional mechanisms to explain the putative sex difference in the susceptibility to carcinogens in tobacco smoke. 1) Among the many carcinogens contained in tobacco smoke, the polycyclic aromatic hydrocarbons (PAHs) are believed to play major roles in the development of lung cancer among smokers. Examination of aromatic/hydrophobic DNA adducts (predominantly PAH adducts) in normal lung tissues of male and female lung cancer patients who were current smokers revealed statistically significantly higher levels of adducts in women than in men after adjustment for either the cumulative lifetime pack-years of smoking or the number of cigarettes smoked per day *(5,31).* 2) The CYP1A1 gene, a member of the P-450 gene family, is believed to play a central role in the metabolic activation of PAH. Mollerup et al. *(5)* showed that CYP1A1 expression

Table 4. Geometric mean (95% confidence interval) levels of 3- and 4-aminobiphenyl (ABP)–hemoglobin adducts (pg/g hemoglobin)* by sex and smoking status at blood draw

	No. of cigarettes/day					
	Men			Women		
	0	1–19	⩾20	0	1–19	⩾20
Case patients and control subjects*	781	109	149	228	25	32
Average No. of cigarettes/day	0	7.9	27.3	0	7.9	23.3
3-ABP–hemoglobin adducts†	0.40 (0.34 to 0.46)	3.21 (2.50 to 4.06)	5.42 (4.52 to 6.45)	0.41 (0.30 to 0.52)	5.88 (3.72 to 9.03)	6.61 (5.0 to 8.66)
4-ABP–hemoglobin adducts†	24.77 (23.45 to 26.17)	60.32 (52.08 to 69.85)	91.39 (82.53 to 101.20)	24.93 (22.47 to 27.66)	89.32 (72.12 to 110.55)	109.60 (94.99 to 126.44)
Control subjects only*	428	53	57	127	8	11
Average No. of cigarettes/day	0	6.5	26.5	0	6.4	21.8
3-ABP–hemoglobin adducts‡	0.30 (0.25 to 0.36)	1.84 (1.27 to 2.55)	4.38 (3.33 to 5.70)	0.30 (0.21 to 0.40)	1.86 (0.45 to 4.63)	5.25 (2.93 to 8.94)
4-ABP–hemoglobin adducts‡	21.41 (20.26 to 22.61)	44.01 (36.65 to 52.81)	78.15 (68.55 to 89.06)	22.59 (20.05 to 25.45)	67.39 (45.11 to 100.44)	92.50 (72.70 to 117.63)

*Number of subjects. The sum is less than the total number of case patients because of the exclusion of subjects with missing values in the analysis.

†The geometric mean level and 95% confidence intervals are provided. The *P* values for sex differences in the slopes of regression lines of 3- and 4-ABP–hemoglobin adducts by cigarettes smoked per day were <.001 and .006, respectively. Statistical tests were two-sided.

‡The geometric mean level and 95% confidence intervals are provided. The *P* values for sex differences in the slopes of regression lines of 3- and 4-ABP–hemoglobin adducts by cigarettes smoked per day were .005 and .03, respectively.

levels in the normal lung tissues of female smokers were substantially higher than those in male smokers. They also demonstrated a statistically significant positive correlation between the CYP1A1 expression level and the aromatic/hydrophobic DNA adduct level in normal lung tissues of their 27 (12 males and 15 females) lung cancer patients who were current smokers. Thus, the observed sex difference in smoking-related lung cancer risk may be explained, at least in part, by a possible difference in CYP1A1 expression in the target tissues. Possible mechanisms underlying the putative sex variation in CYP1A1 expression are unknown. However, *in vitro* studies [reviewed in *(5)*] have suggested complex interactions between the estrogen receptor and the aryl hydrocarbon receptor pathways. 3) In normal lung tissue, gastrin-releasing peptide promotes cell proliferation of lung epithelia, and there is evidence that it participates in lung cancer development *(4)*. The effect of gastrin-releasing peptide is mediated partly through an interaction with the gastrin-releasing peptide receptor, the gene for which is located on the X chromosome and escapes X-chromosome inactivation in females *(32)*. Shriver et al. *(4)* compared gastrin-releasing peptide receptor gene expression in normal lung tissue samples from 40 men and 38 women and found considerably higher gene expression in women than in men, regardless of smoking status. The authors hypothesized that the expression of both copies of the gastrin-releasing peptide receptor gene in women (versus a single copy in men) might be a factor in the putative increased risk of lung cancer observed in women *(4)*.

Besides the lung, the bladder is another recognized site susceptible for tobacco carcinogenesis in humans. Indeed, it is believed that at least 50% of bladder cancers in U.S. men are related to cigarette smoking *(2)*. Before the present study, to our knowledge, there have been five case–control studies examining the sex-specific risk of bladder cancer in cigarette smokers *(14,15,20,33,34)*. However, in the only study to perform statistical analysis for any possible sex difference, Burch et al. *(20)* did not observe a statistically significant interaction between lifetime cigarette use and sex ($P = .13$), although, among heavy smokers (≥40 pack-years of smoking), the risk of bladder cancer in women was close to twofold that in men (OR = 4.88 [95% CI = 2.11 to 11.27] versus OR = 2.40 [95% CI = 1.64 to 3.50], respectively). Morrison et al. *(15)* investigated cigarette smoking and the risk of bladder cancer in three cities—Boston (MA), Nagoya (Japan), and Manchester (U.K.). In both Boston and Nagoya, the ORs for bladder cancer risk in female smokers were two or more times higher than those in male smokers, although, on average, women in both cities smoked fewer cigarettes per day than men. By contrast, the OR for bladder cancer risk in female smokers from Manchester was comparable to that in male smokers (OR = 1.3 [95% CI = 0.8 to 2.0] versus OR = 2.2 [95% CI = 1.4 to 3.5]). In other studies *(14,33,34),* similar ORs for bladder cancer risk were noted in male and female smokers.

Case–control data alone are insufficient to address the question of differential sex-specific susceptibility to tobacco carcinogenesis. In other words, one cannot conclude that women are more susceptible to the carcinogenic effects of tobacco based only on the observation that there is a larger relative risk estimate in women than in men who smoke comparable amounts of cigarettes *(35)*. For example, under the assumption of a lower baseline risk in nonsmoking women than in nonsmoking men and a constant additive risk of bladder cancer associated with smoking, one would expect to observe a larger relative risk in women than in men at a given level of smoking. Despite the weakness of a case–control study, our results are, however, strengthened by the addition of corroborating evidence regarding 3- and 4-ABP–hemoglobin adducts in women who smoke. Consistent with differential sex-specific susceptibility to tobacco carcinogens, we noted that women who smoked had statistically significantly higher levels of 3- and 4-ABP–hemoglobin adducts compared with men who smoked comparable amounts of cigarettes. Thus, women may experience a higher degree of arylamine activation compared with men and, consequently, have a higher risk of bladder cancer.

There is little information on sex-specific patterns of arylamine activation. Nonetheless, it is interesting to note that glutathione *S*-transferase M1 (GSTM1), a detoxification enzyme linked to a low risk of bladder cancer *(2),* is more abundant in male than in female mouse livers *(36)*. This experimental result would predict that there is higher arylamine detoxification activity as well as lower arylamine adduct formation and, consequently, a lower risk of bladder cancer in male than in female smokers. In a preliminary analysis, we assessed the genotype for arylamine–metabolizing enzymes, including GSTM1, in 485 male and 126 female non-Hispanic control subjects from the present case–control study. There were no statistically significant differences in the genotypes between men and women for GSTM1, *N*-acetyltransferase-1, *N*-acetyltransferase-2, glutathione *S*-transferase-P1, glutathione *S*-transferase-T1, or cytochrome P4501A2 (data not shown).

Our study also benefited from a large sample size, which allowed for an in-depth examination of bladder cancer risk in smokers grouped by cigarette composition and pattern of inhalation. After controlling for both duration and intensity of cigarette smoking, we did not observe any statistically significant difference in the risk of bladder cancer between users of filtered versus nonfiltered cigarettes, of low-tar versus higher tar cigarettes, or of different self-reported depths of inhalation.

Previous epidemiologic studies on the use of filtered versus nonfiltered cigarettes and the risk of bladder cancer have had varied results. Most studies *(14,15, 19–22,37,38)* have reported no statistically significant reduction in risk of bladder cancer in smokers of filtered compared with nonfiltered cigarettes, although a few studies *(16,17,24)* have found a reduction. For example, Vineis et al. *(16)* observed a reduced risk in smokers of filtered versus nonfiltered cigarettes, independently of the number of cigarettes smoked and years since smoking cessation. Hartge et al. *(17)* noted a reduced risk of bladder cancer between filtered versus nonfiltered cigarette use only among current smokers. Finally, Cartwright et al. *(24)* found that smokers of filtered cigarettes had no increased risk of bladder cancer compared with nonsmokers (OR = 1.05; 95% CI = 0.73 to 1.51), while smokers of nonfiltered cigarettes had a slight increased risk (OR = 1.36; 95% CI = 1.07 to 1.73). In addition, Dallinga et al. *(39)* examined 4-ABP–hemoglobin adducts in smokers and found no association between adducts and filter status of cigarettes smoked. However, because most filtered cigarette use occurred after 1960 *(40),* confounding of calendar time with different cigarette types limits any interpretation of results

regarding filtered and nonfiltered cigarette use.

Experimental studies *(41,42)* have shown that low-tar cigarettes are no less mutagenic to human bladder urothelium than higher tar cigarettes. Our data support these previous studies because we detected no difference in the risk of bladder cancer between smokers of low-tar versus higher tar cigarettes. To our knowledge, only one prior epidemiologic study examined use of low-tar cigarettes and bladder cancer risk *(22).* The authors of that study reported a decrease in risk with use of low-tar, low-nicotine cigarettes.

Our study also found no clear association between self-reported depth of inhalation and the risk of bladder cancer. This finding agrees with prior case–control data from Howe et al. *(14),* Hartge et al. *(17),* and Probert et al. *(38).* By contrast, some case–control studies *(15,18,20–22)* have reported a higher bladder cancer risk among smokers who inhaled deeply. These conflicting results may be due to the subjective and perhaps somewhat unreliable nature of self-reporting smoking patterns.

In summary, we did not observe any difference in the risk of bladder cancer among users of filtered versus nonfiltered cigarettes or low-tar versus higher tar cigarettes or for self-reported degrees of inhalation. However, our large case–control study provides the first evidence, to our knowledge, that, when comparable numbers of cigarettes are smoked, the risk of bladder cancer may be higher in women than in men.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, poulation-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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