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Environmental Tobacco Smoke in Relation to Bladder Cancer Risk – The Shanghai Bladder Cancer Study

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Abstract

Background—Environmental tobacco smoke (ETS) contains tobacco carcinogens. Hepatic cytochrome P450 (CYP) 1A2 and *N*-acetyltransferase (NAT2) are important isoenzymes in activation and detoxification, respectively, of tobacco carcinogens. Data on ETS and bladder cancer risk are sparse.

Methods—We examined the effects of ETS alone and combined with NAT2/CYP1A2 on bladder cancer risk among lifelong-nonsmokers in a case-control study involving 195 patients and 261 controls in Shanghai, China. A comprehensive history of ETS exposure was determined through in-person interviews while CYP1A2 and NAT2 phenotypes by a caffeine-based urinary assay.

Results—ETS exposure was related to an overall statistically non-significant 38% increased bladder cancer risk. The risk increased with increasing number of cigarettes smoked by household members or number of hours per day at workplace where coworkers smoked. Compared with no ETS exposure, subjects living with smoking parents during childhood had an OR of 2.43 (95% CI=0.99–5.96) for bladder cancer. When all ETS sources were combined, the risk increased with increasing total ETS score ($P_{trend} = 0.03$). The OR for high versus nil ETS exposure was 3.00 (95% CI = 1.24–7.26). The increased risk with ETS was mainly seen among individuals possessing a CYP1A2 high efficiency and/or a NAT2 slow acetylation phenotype ($P_{trend} = 0.04$).

Conclusions—ETS was associated with an increased bladder cancer risk for lifelong-nonsmokers. The association was stronger for people possessing the at-risk phenotypes of CYP1A2 and/or NAT2.

Impact—Reducing exposure to ETS for children and genetically more susceptible individuals could be more effective for bladder cancer prevention.

INTRODUCTION

Bladder cancer is a common cancer in the United States (US). The incidence rates of bladder cancer in men and women were 38.4 and 9.8 per 100,000 persons per year in US, respectively, during 2001–2005 (1). In contrast, the incidence rate is low in Asian populations. Bladder cancer rates for men and women in Shanghai, China, were 6.18 and 1.90 per 100,000 persons per year, respectively, during 1993–1997 (2). Cigarettes smoking is an established cause of bladder cancer, accounting for approximately 50% of the disease burden in the US and other Western countries(3,4). Smokers generally double their risk for developing bladder cancer compared to non-smokers (5,6). Certain arylamines, including 2-naphthylamine and 4-aminobiphenol (4-ABP) present in tobacco smoke and other environmental sources are Group 1 human bladder carcinogens, as defined by the International Agency for Research on Cancer (3,7).

Arylamines require metabolic activation to exert their carcinogenic effects. Hepatic cytochrome P450 1A2 (CYP1A2) is a critical isoenzyme to catalyze the first step in the metabolic activation pathway of the precarcinogenic arylamines (8). Our recent analysis demonstrated that the CYP1A2 phenotype score was a strong risk determinant of bladder cancer among smokers (9). On the other hand, hepatic *N*-acetyltransferases (NATs) detoxify various tobacco toxicants including arylamines. Numerous epidemiologic studies have shown a statistically significantly elevated risk of bladder cancer for individuals with slow acetylation status (10–12).

Environmental tobacco smoke (ETS) contains detectable levels of several tobacco carcinogens including certain arylamines (13,14). Nonsmokers who were exposed to ETS showed higher levels of biomarkers of tobacco carcinogens including 4-ABP compared to nonsmokers without ETS exposure (15–17). Therefore, exposure to ETS may confer risk of bladder cancer. Previous studies reported inconsistent results on the association between ETS exposure and bladder cancer. Some found a positive ETS-bladder cancer risk association (18–20), whereas others reported null results (21–27). This ambiguity might be due to the inherent measurement error of ETS and low levels of potential bladder carcinogens present in ETS. In the present analysis, we examined the risk of bladder cancer among lifelong nonsmokers on whom a history of exposure to ETS was assessed over the lifecourse. Furthermore, we evaluated whether a set of genetic risk factors for bladder cancer, including CYP1A2 and NAT2 phenotypes, might modify the ETS-bladder risk cancer association.

METHODS

Study population

Bladder cancer patients were identified through the Shanghai Cancer Registry, a population-based cancer registry covering the approximately 8 million residents of urban area in Shanghai, China, in the 1990's. The registry identified 708 patients aged 25 to 74 years who were diagnosed with bladder cancer from 1st July 1995 through 30th June 1998. Among them, 56 patients died before we could contact them, 29 refused to be interviewed, and 42 were unable to be located. We interviewed the remaining 581 (82%) eligible patients between July 1996 and June 1999. The diagnosis of bladder cancer for 531 (91%) patients was made based on histopathological evidence whereas the remaining 50 (9%) patients' diagnoses were based on positive computerized axial tomography scan and/or ultrasonograph with consistent clinical history.

Control subjects were randomly selected from urban residents of Shanghai and chosen to match the frequency distribution by sex and 5-year age groups of bladder cancer patients as

ascertained by the Shanghai Cancer Registry during 1990–1994. Personal identification cards issued by the Shanghai Municipal Government were used to select potential control subjects. These cards, one per resident, were housed in 4,410 file cabinet drawers (which were numbered from 1 to 4,410 at the Resident Registry, Bureau of Public Security of Shanghai). We generated 750 random numbers between 1 and 4470. The number of 750 was our anticipated number of incident bladder cancer cases during the three years of case ascertainment period (7/1/95~6/30/98) of the study. We were unable to locate 74 subjects due to their change of home addresses. Seventy-two subjects refused to participate in the study. We interviewed the remaining 604 (80%) subjects during July 1996 and June 1999.

Data collection

Study was approved by the Shanghai Cancer Institute, the University of Southern California, and the University of Minnesota. After obtaining a written informed consent from each eligible study subject, a trained interviewer administered an in-person interview to the subject by using a structured questionnaire that solicited information on demographic characteristics, history of tobacco use, consumption of beverages including alcohol, coffee, tea, soft drinks and plain water, use of hormones (for women only), medical history, usual adult diet, and occupational history. The questionnaire asked for the information on environmental exposures that took place from the beginning of a subject's life until 2 years prior to the diagnosis of bladder cancer for case patients or 2 years prior to the date of interview for control subjects (reference date). We excluded information on exposure that occurred within 2 years of bladder cancer diagnosis due to the concern on the changes of patients' lifestyles, including cigarettes smoking, rendered by subclinical symptoms of the cancer. Similarly, we excluded the exposure information for control subjects in the corresponding time period. Among 581 interviewed cases and 604 interviewed controls, 379 cases and 336 controls self reported use of any tobacco product (cigarettes, water pipes, or dry pipes) daily for six months or longer, the remaining 202 cases and 268 controls were defined as lifelong nonsmokers.

For lifelong nonsmokers, the study questionnaire further asked for the smoking history of their mother, father, spouse(s), and other relatives (including offspring, siblings, grandparents, aunts/uncles, and in-laws) who ever lived in the same household as the study subject. For each smoking family member or relative, we asked about the beginning and ending years of smoking, the total number of years of smoking while living with the study subject, and the number of cigarettes smoked per day at home during that time period. In addition, subjects were asked to provide information on the smoking habits of coworkers in an indoor environment. For each job held with coworkers who smoked during work, we asked about the beginning and ending years of that job, and the number of hours per day that the subject was exposed to ETS at work.

All study subjects were asked to donate blood and urine samples at the end of the in-person interview. Forty-six case patients and 61 control subjects refused to collect their overnight urine samples. Prior to the collection of an overnight urine sample, each consenting subject was given two packets of Nestle instant coffee or two cans of Coca-Cola Classic drink (about 70 mg of caffeine) to be drunk between 3 and 6 pm. The subject then collected an overnight urine sample (ending with the first morning void) into a plastic jar that was picked up by the same interviewer in the following morning. The urine samples were processed, acidified (400 mg of ascorbic acid per 20 mg of urine), and stored at -80°C on the same day of urine pickup until analysis.

Phenotyping

CYP1A2 and NAT2 phenotype status were determined by the ratios of specific caffeine metabolites in the overnight urine samples. Urinary caffeine metabolites, namely 5-acetylamino-6-amino-3-methyluracil (AAMU), 1-methylxanthin (MX), 1-methyluric acid (MU) and 1,7-dimethylxanthin (17X), were measured using the modified procedure of Tang *et al.* (28). Quantification of MX, MU and 17X in urine was performed according to a modified procedure of Grant *et al.* (29). The CYP1A2 phenotype score was determined based on a ratio of urinary caffeine metabolites, *i.e.* (AAMU + MX + MU)/17X (29). Higher values of the CYP1A2 phenotype score reflect higher CYP1A2 activities. We used the median value of the CYP1A2 phenotype score in all lifelong nonsmoking controls to classify subjects into high (≥ 5.11) or low (< 5.11) CYP1A2 phenotype activity status. Similarly, based on the ratio of urinary metabolites of caffeine, *i.e.* AAMU/(AAMU+MX+MU), subjects were classified as either slow (ratio < 0.34) or rapid (ratio ≥ 0.34) NAT2 acetylators (30). The caffeine metabolites for the calculation of the CYP1A2 or NAT2 phenotype scores were undetectable in urine samples of 5 cases and 18 control subjects.

Statistical analysis

For the present analysis, we excluded 14 self-reported lifelong nonsmokers (7 cases and 7 controls) whose urinary levels of cotinine were greater than 75 ng/ml. Thus the primary analysis included 195 bladder cancer patients (97 women) and 261 control subjects (128 women). In the analyses stratified by CYP1A2 and/or NAT2 phenotype status, we excluded additional 22 cases (17 did not donate urine samples and 5 had undetectable urinary caffeine metabolites) and 44 controls (26 did not donate urine samples and 18 had undetectable urinary caffeine metabolites) with unknown CYP1A2 or NAT2 phenotype scores.

The chi-square test was used to examine differences in the distributions of categorical variables between case patients and control subjects and by ETS exposures among control subjects only, while the *t*-test was used to examine the difference in means of continuous variables. Among all the categorical variables we examined, ETS exposure was significantly or borderline significantly associated with age at reference year ($P = 0.09$), the level of education ($P = 0.07$), and consumption of tea ($P = 0.05$) and cruciferous vegetables ($P = 0.002$). Other factors were comparable for control subjects with or without ETS exposure (all $P > 0.05$). We used unconditional logistic regression models to estimate the odds ratio (OR) and its confidence interval (CI) for bladder cancer associated with ETS exposure (31). The strength of the association between ETS exposure and bladder cancer risk was evaluated by the OR, its 95% CI and associated *P* value. Age at reference date (continuous), gender, level of education (no formal schooling, primary school, middle school, and college and above), and consumption of tea (yes/no) and cruciferous vegetables (< 3 times per week/ ≥ 3 times per week) were included as covariates in all regression models.

For each subject, a composite index denoting total ETS exposure over subject's lifetime was constructed as follows. For each member of the household, a score of 0, 1, or 2 was assigned depending on whether he/she smoked 0 (nonsmoker), 1– <10 , or ≥ 10 cigarettes per day. For exposure to ETS at work, no exposure was assigned a score of zero, 1– <5 hours per day was assigned a score of 1, and ≥ 5 hours per day was assigned a score of 2. We then summed all scores (each has a range of 0–2) from the five sources of ETS (mother smoked, father smoked, spouse smoked, other household member smoked, coworker smoked). The index of total ETS exposure thus has a score that can range from zero to 10.

Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) statistical software package. All *P* values are two sided. *P* values less than 0.05 were considered statistically significant.

RESULTS

The present study included 195 bladder cancer cases and 261 control subjects who were lifelong nonsmokers. The mean age (standard deviation) of case patients was 60.5 (10.1) years whereas the mean age of control subjects was 62.1 (9.9) years at reference date ($P = 0.08$). Fifty percent of case patients and a similar percentage of control subjects were women ($P = 0.88$). Case patients had similar distributions as controls by level of education, consumption of alcohol, coffee and tea, intake of cruciferous vegetables, use of oral contraceptives for women, family history of cancer, and high-risk jobs held (Table 1). Among control subjects, ETS exposure was significantly associated with level of education and consumption of tea and cruciferous vegetables. We did not find a statistically significant relation of ETS exposure with any other factors listed in Table 1 among control subjects (data not shown).

Table 2 shows the odds ratios of bladder cancer associated with ETS exposure by different sources. Eighty-four percent of bladder cancer cases and 79% of control subjects reported ever having been exposed to ETS at home or at workplace. Overall, exposure to ETS was related to a statistically non-significant increase in bladder cancer risk (OR=1.38, 95% CI = 0.85 – 2.26). The strength of the ETS-bladder cancer association varied according to the source of ETS. Living with both parents who were smokers during childhood had a statistical borderline significant increased risk for bladder cancer (OR=2.43, 95% CI = 0.99 – 5.96) among total subjects, and a statistically significant increased risk among women (OR = 6.87, 95% CI = 1.48 – 31.95). The OR of bladder cancer increased with increasing number of cigarettes smoked per day by the mother. Compared with no ETS exposure, maternal heavy smoking (≥ 10 cigarettes per day) was associated with an OR of 3.23 (95% CI = 0.96–10.83). Subjects who worked with smoking coworkers in an indoor environment for 5 or more hours a day doubled their risk of bladder cancer as compared to those with no ETS exposure (OR = 2.38, 95% CI = 1.14–4.95). When all sources of ETS were combined, there was a statistically significant, monotonically increased risk of bladder cancer associated with increasing ETS exposure index ($P_{trend} = 0.03$) after adjustment for potential confounders. The OR for high (index score of 5 or more) versus nil total ETS exposure was 3.00 (95% CI = 1.24 – 7.26) (Table 2). The association between ETS exposure and bladder cancer risk was stronger in women than men, although this gender difference was not statistically significant.

Table 3 shows the association between the index of total ETS exposure and bladder cancer risk stratified by CYP1A2 phenotype, NAT2 phenotype, and the two phenotypes combined. Among subjects possessing the CYP1A2 high efficiency phenotype (scores above the median value), ORs increased with increasing ETS index scores ($P_{trend} = 0.09$). High versus nil total ETS exposure had an OR of 3.17 (95% CI = 0.90 – 11.18) for bladder cancer. Among individuals possessing rapid NAT2 phenotype status, the OR is 3.22 (95% CI = 1.06–9.84) for those exposed with high level of ETS as compared to those with no ETS exposure. When CYP1A2 and NAT2 phenotypes were examined simultaneously, only subjects possessing at least one of the two at-risk phenotypes experienced an increased risk of bladder cancer ($P_{trend} = 0.04$), after adjustment for potential confounders. Among subjects possessing the low-risk phenotypes of CYP1A2 and NAT2, there was no evidence of an association between ETS exposure and bladder cancer risk ($P_{trend} = 0.57$).

DISCUSSION

The present study suggests an elevated risk of bladder cancer in lifelong nonsmokers who were exposed to ETS as compared with those who had no ETS exposure. The risk increased with increasing intensity of exposure to ETS, and reached statistically significant levels for

high level of exposure to ETS. In the subgroup analysis, female lifelong nonsmokers showed higher relative risk for bladder cancer associated with ETS exposure than their male counterparts, and so did individuals possessing high CYP1A2 phenotype score and/or NAT2 slow acetylation status, both of them were risk factors for bladder cancer in the present study population (9).

Previous epidemiological studies on ETS and bladder cancer risk reported inconsistent results. Several studies reported a null association between ETS and bladder cancer risk (21–26) including a recent meta-analysis (13), whereas a few others found a positive association (18–20). The null findings of the previous studies could be due to the following reasons. It has been shown that the dose of carcinogenic arylamines in secondhand smokers was only 0.3–0.5% that of active smokers (14,17). Given the low levels of potential tobacco bladder carcinogens present in ETS, one would expect a moderate association between ETS and bladder cancer. Furthermore, a relatively large error in measurement of ETS for a given individual over lifetime could mask the moderate effect of ETS on bladder cancer risk. In addition, most of those studies lacked statistical power because of relatively small sample sizes. The present study employed a more comprehensive approach to assess the ETS exposure for each individual, which could reduce the measurement error. The relatively large sample size (195 cases and 261 controls) of the present study allowed for the detection of a moderate effect of ETS on bladder cancer. More importantly, the determination of genetic susceptibility to bladder cancer would identify more vulnerable individuals to ETS and could clarify the association between ETS and bladder cancer.

The present study showed that female lifelong nonsmokers who were exposed to ETS, especially at the high level of ETS exposure, had higher relative risk for bladder cancer than their male counterparts. This result was consistent with our previous study showing that women experienced higher risk for bladder cancer than men although they smoked comparable amount of cigarettes (32). We also showed a stronger ETS-bladder cancer risk association in female lifelong nonsmokers in Los Angeles than their male counterparts in our previous report (18). In the same report we demonstrated that women with current ETS exposure were 9 times more likely than men to possess elevated hemoglobin adduct level of 4-ABP, a risk predictor for bladder cancer among lifelong nonsmokers.

The high risk of bladder cancer associated with ETS from parental smoking suggested that exposure to ETS that took place during childhood might be more harmful than exposure during adulthood. In our previous report based on the Los Angeles Bladder Cancer Study, women who ever lived with two or more smokers during childhood experienced a statistically significant 3-fold increased risk for bladder cancer whereas no risk increase was associated with ETS exposure in adulthood (18).

Genetically determined factors can potentially modify the association of ETS exposure with risk of developing cancer. A few epidemiology studies have shown that polymorphisms of NAT2, CYP1A1, or glutathione *S*-transferase M1 (GSTM1) could modify the association between ETS exposure and risk of lung cancer in lifelong nonsmokers (33–35). Although the overall association between ETS exposure and bladder cancer risk was moderate, the present study demonstrated a stronger association in lifelong nonsmokers possessing either a high efficiency CYP1A2 phenotype or a NAT2 slow acetylation phenotype, both of which have been associated with an increased risk of bladder cancer (8,9,36). Our findings of an association between ETS exposure and bladder cancer risk, which became stronger among individuals either efficient in activating or deficient in detoxifying the putative bladder carcinogens in tobacco smoke, have important public health implications.

The strengths of the present study included a population-based study design, comprehensive approach to assess ETS exposure over lifetime, a relatively large sample size, and the determination of two important genetic risk factors for bladder cancer. A relatively large sample size of female lifelong nonsmokers given the low smoking prevalence in Chinese women in Shanghai (6% in female controls of the present study) enabled us to examine the association between ETS exposure and risk of bladder cancer in men and women separately. Although the study data was collected more than 10 years ago, our findings are still relevant to current public health in China, since the prevalence of smoking in men (63%) and women (4%) in China over the past 15 years have been remarkable stable; the change in rate of smoking between 1996 and 2002 was under 1% (37,38). A potential weakness of the study was the possible recall bias in measuring ETS, inherent in any retrospective studies, which could lead to a spurious association between ETS and bladder cancer risk. However, given the stronger ETS-bladder cancer association among the genetically more susceptible subpopulation as predicted by well recognized biochemical models of tobacco smoking (36), it is unlikely that the observed ETS-bladder cancer risk association was the result of recall bias.

The findings of the present study have important public health implications for the US population. For example, the present study demonstrates that ETS exposure in childhood was more harmful than that in adulthood. It is estimated that 40% of children worldwide and 37% of children in the US are exposed to ETS at home (39,40). Thus, strategies aim at reducing or eliminating ETS exposure among children could lead to a lower bladder cancer burden in the next generation. This study also showed that the risk effect of ETS on bladder cancer was primarily confined to individuals possessing an unfavorable phenotype of either CYP1A2 or NAT2. In the US, over 50% of Caucasians possess the NAT2 slow acetylation phenotype (41). Therefore, cancer prevention efforts targeting more susceptible subpopulation could be more cost-effective in reducing the population burden of bladder cancer.

In summary, the present study demonstrates a positive association between high level of ETS exposure and risk of bladder cancer. The study also shows a stronger ETS-bladder cancer association among individuals possessing the at-risk phenotypes of CYP1A2 and NAT2, which are recognized to participate in the metabolism of putative bladder carcinogens in tobacco smoke.

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Table 1

Distributions of selected characteristics among lifelong nonsmokers by disease status, The Shanghai Bladder Cancer Case-Control Study

	No. cases (%)	No. controls (%)	2-sided <i>P</i>
Total	195 (100)	261 (100)	
Age at reference year			0.378
<50	27 (13.9)	26 (10.0)	
50–<60	38 (19.5)	47 (18.0)	
60–<70	102 (52.3)	138 (52.9)	
≥70	28 (14.4)	50 (19.2)	
Gender			0.882
Males	98 (50.3)	133 (51.0)	
Females	97 (49.7)	128 (49.0)	
Education			0.411
No formal schooling	29 (14.9)	34 (13.2)	
Primary school	41 (21.0)	60 (23.0)	
Middle school	65 (33.3)	102 (39.1)	
College and above	60 (30.8)	65 (24.9)	
Body mass index, kg/m ²			0.291
<18.5 (underweight)	12 (6.2)	19 (7.3)	
18.5–24.9 (normal)	138 (70.8)	197 (75.5)	
≥25 (overweight and obese)	45 (23.1)	45 (17.2)	
Ever drink alcohol on a regular basis *			0.486
Yes	31 (15.9)	48 (18.4)	
No	164 (84.1)	213 (81.6)	
Ever drink tea on a regular basis *			0.278
Yes	68 (35.9)	104 (39.9)	
No	127 (65.1)	157 (60.2)	
Ever drink coffee on a regular basis *			0.750
Yes	5 (2.6)	8 (3.1)	
No	190 (97.4)	253 (96.9)	
Ever take cruciferous vegetables on a regular basis †			0.797
Yes	178 (91.3)	240 (92.0)	
No	17 (8.7)	21 (8.1)	
Ever held a high-risk job ‡			0.360
Yes	12 (6.2)	22 (8.4)	
No	183 (93.9)	239 (91.6)	
Ever used hormones (female only)			0.764
Yes	15 (15.5)	20 (15.6)	
No	82 (85.5)	108 (84.4)	
Any close relatives ever had cancer			0.262
Yes	53 (27.2)	59 (22.6)	

	No. cases (%)	No. controls (%)	2-sided <i>P</i>
No	142 (72.8)	202 (77.4)	
CYP1A2 phenotype score [§]			0.107
Low (<5.11)	74 (42.8)	107 (49.3)	
High (≥5.11)	99 (57.2)	110 (50.7)	
NAT2 phenotype score [§]			0.151
Rapid (≥0.34)	135 (78.0)	178 (82.0)	
Slow (<0.34)	38 (22.0)	39 (18.0)	

* Alcohol, tea, and coffee consumption on a regular base were defined as drinking the beverage at least once per week for 6 months.

[†] Cruciferous vegetable intake on a regular basis was defined as taking bokchoi, cabbage, or cauliflower at least 3 times per week.

[‡] A subject who had ever held a high risk job was defined as ever been a painter, textile dyer, printer, chimney sweeper, leather product worker, or glass worker for more than a year.

[§] Twenty-two cases and 44 controls with missing value of CYP1A2 or NAT2 phenotype score were excluded from these analyses.

Exposure to environmental tobacco smoke in relation to risk of bladder cancer among lifelong nonsmokers, The Shanghai Bladder Cancer Study

Table 2

Exposure to ETS	Total		Men		Women	
	No. Ca/Co	OR (95% CI) *	No. Ca/Co	OR (95% CI) *	No. Ca/Co	OR (95% CI) *
No	32/56	1.00 (ref)	21/31	1.00 (ref)	11/25	1.00 (ref)
Yes	163/205	1.38 (0.85–2.26)	77/102	1.21 (0.63–2.32)	86/103	1.83 (0.82–4.05)
Parental smoking						
Father smoked only	60/85	1.23 (0.71–2.16)	27/42	1.07 (0.50–2.28)	33/43	1.72 (0.72–4.15)
Mother smoked only	10/15	1.22 (0.48–3.08)	6/4	2.19 (0.53–9.06)	4/11	0.82 (0.20–3.42)
Both parents smoked	16/11	2.43 (0.99–5.96)	6/8	0.91 (0.27–3.11)	10/3	6.87 (1.48–31.95)
Father smoked	76/96	1.36 (0.78–2.35)	33/50	0.94 (0.44–1.97)	43/46	2.22 (0.90–5.44)
No. of Cigarettes per day						
1–<10	37/44	1.39 (0.73–2.63)	15/18	1.17 (0.47–2.93)	22/26	1.95 (0.72–5.29)
≥10	39/52	1.33 (0.71–2.47)	18/32	0.80 (0.34–1.85)	21/20	2.54 (0.92–6.96)
Mother smoked	26/26	1.59 (0.75–3.37)	12/12	0.89 (0.29–2.71)	14/14	3.67 (0.99–13.52)
No. of Cigarettes per day						
1–<10	16/21	1.20 (0.52–2.78)	7/9	0.48 (0.13–1.78)	9/12	2.52 (0.62–10.26)
≥10	10/5	3.23 (0.96–10.83)	5/3	3.14 (0.51–19.37)	5/2	15.97 (1.62–157.30)
Spouse smoked	53/70	1.31 (0.72–2.39)	3/6	0.47 (0.08–2.59)	50/64	1.84 (0.80–4.25)
No. of Cigarettes per day						
1–<10	24/37	1.14 (0.56–2.31)	3/3	0.93 (0.13–6.59)	21/34	1.44 (0.56–3.66)
≥10	29/33	1.50 (0.75–3.01)	0/3	–/–	29/30	2.27 (0.92–5.62)
Other household members smoked	58/61	1.57 (0.88–2.81)	29/30	1.38 (0.63–3.00)	29/31	1.83 (0.72–4.67)
No. of Cigarettes per day						
1–<10	41/50	1.40 (0.76–2.58)	21/23	1.30 (0.55–3.03)	20/27	1.57 (0.59–4.14)
≥10	17/11	2.40 (0.96–6.02)	8/7	1.64 (0.47–5.69)	9/4	3.62 (0.82–16.05)
Co-workers smoked	74/100	1.27 (0.70–2.30)	49/72	1.05 (0.51–2.14)	25/28	1.65 (0.50–5.39)
No. of hours smoked per day						
1–<5	39/72	0.91 (0.48–0.73)	27/53	0.74 (0.34–1.60)	12/19	1.46 (0.41–5.15)
≥5	35/28	2.38 (1.14–4.95)	22/19	2.00 (0.83–4.86)	13/9	2.10 (0.49–9.10)

Exposure to ETS	Total		Men		Women	
	No. Ca/Co	OR (95% CI) *	No. Ca/Co	OR (95% CI) *	No. Ca/Co	OR (95% CI) *
Combined index of ETS †						
No exposure	32/56	1.00 (ref)	21/31	1.00 (ref)	11/25	1.00 (ref)
1–4 (low)	144/194	1.30 (0.79–2.14)	68/96	1.15 (0.59–2.21)	76/98	1.75 (0.79–3.89)
5+ (high)	19/11	3.00 (1.24–7.26)	9/6	2.08 (0.63–6.92)	10/5	3.89 (0.98–15.47)
<i>P_{trend}</i>		0.030		0.311		0.051

* Odds ratios (ORs) were adjusted for age at reference date (continuous), education level (no formal schooling, primary school, middle school, and college and above), and consumption of tea (yes/no) and cruciferous vegetables (< 3 times per week/ ≥ 3 times per week); CI=confidence interval.

† See the Methods section for the definition of the combined index of ETS.

Table 3

Exposure to environmental tobacco smoke in relation to risk of bladder cancer among lifelong nonsmokers stratified by CYP1A2 phenotype score and NAT2 acetylation status, The Shanghai Bladder Cancer Study

	Never exposed		Ever exposed		Among Ever exposed				<i>P</i> _{trend} [*]
					Combined index of ETS 1–4 (Low) [*]		Combined index of ETS 5+ (High) [*]		
	No. Ca/Co	OR (95%CI) [†]	No. Ca/Co	OR (95%CI) [†]	No. Ca/Co	OR (95%CI) [†]	No. Ca/Co	OR (95%CI) [†]	
CYP1A2 phenotype score									
Low (<5.11)	15/22	1.00 (ref)	59/85	1.17 (0.53–2.60)	52/80	1.10 (0.49–2.45)	7/5	3.20 (0.76–13.51)	0.239
High (≥5.11)	15/24	1.00 (ref)	84/86	1.49 (0.72–3.07)	73/81	1.37 (0.66–2.86)	11/5	3.17 (0.90–11.18)	0.093
NAT2 phenotype score									
Rapid (≥0.34)	24/35	1.00 (ref)	111/143	1.11 (0.61–2.01)	96/137	1.02 (0.56–1.86)	15/6	3.22 (1.06–9.84)	0.141
Slow (<0.34)	6/11	1.00 (ref)	32/28	2.46 (0.74–8.21)	29/24	2.53 (0.75–8.54)	3/4	1.89 (0.27–13.47)	0.280
Combined phenotypes									
CYP1A2 low and NAT2 rapid	13/15	1.00 (ref)	49/74	0.85 (0.34–2.10)	43/71	0.81 (0.33–2.03)	6/3	2.87 (0.51–16.28)	0.570
CYP1A2 high and/or NAT2 slow	17/31	1.00 (ref)	94/97	1.74 (0.89–3.39)	82/90	1.63 (0.83–3.20)	12/7	3.14 (1.02–9.66)	0.041

^{*} See the Methods section for the definitions of the combined index of environmental tobacco smoke (ETS); 22 cases and 44 controls with unknown CYP1A2 and/or NAT2 phenotype scores were excluded from this analysis.

[†] Odds ratios (ORs) were adjusted for gender, age at reference date (continuous), education level (no formal schooling, primary school, middle school, and college and above), and consumption of tea (yes/no) and cruciferous vegetables (< 3 times per week/ ≥ 3 times per week); CI=confidence interval.