Smoking and Bladder Cancer in Spain: Effects of Tobacco Type, Timing, Environmental Tobacco Smoke, and Gender

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Abstract

We examined the effects of dose, type of tobacco, cessation, inhalation, and environmental tobacco smoke exposure on bladder cancer risk among 1,219 patients with newly diagnosed bladder cancer and 1,271 controls recruited from 18 hospitals in Spain. We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between bladder cancer risk and various characteristics of cigarette smoking. Current smokers (men: OR, 7.4; 95% CI, 5.3-10.4; women: OR, 5.1; 95% CI, 1.6-16.4) and former smokers (men: OR, 3.8; 95% CI, 2.8-5.3; women: OR, 1.8; 95% CI, 0.5-7.2) had significantly increased risks of bladder cancer compared with nonsmokers. We observed a significant positive trend in risk with increasing duration and amount smoked. After adjustment for duration, risk was only 40% higher in smokers of black tobacco than that in smokers of blond tobacco (OR, 1.4; 95% CI, 0.98-2.0). Compared with risk in current smokers, a significant inverse trend in risk with increasing time since quitting smoking blond tobacco was observed (≥20 years cessation: OR, 0.2; 95% CI, 0.1-0.9). No trend in risk with cessation of smoking black tobacco was apparent. Compared with men who inhaled into the mouth, risk increased for men who inhaled into the throat (OR, 1.7; 95% CI, 1.1-2.6) and chest (OR, 1.5; 95% CI, 1.1-2.1). Cumulative occupational exposure to environmental tobacco smoke seemed to confer increased risk among female nonsmokers but not among male nonsmokers. After eliminating the effect of cigarette smoking on bladder cancer risk in our study population, the male-to-female incidence ratio decreased from 8.2 to 1.7, suggesting that nearly the entire male excess of bladder cancer observed in Spain is explained by cigarette smoking rather than occupational/environmental exposures to other bladder carcinogens. (Cancer Epidemiol Biomarkers Prev 2006;15(7):1348–54)

Introduction

Cigarette smoking is the best established risk factor for cancer of the urinary bladder. It has been estimated that ~65% of bladder cancer in men and 20% to 30% in women is attributable to cigarette smoking (1). Although cigarette smoking has been causally linked with bladder cancer in numerous studies (1-5), several questions remain regarding the effects of certain smoking-related characteristics.

Some studies have suggested that the international variation in the incidence of risk for bladder cancer may be due to factors such as type of tobacco smoked (2-10). Bladder cancer risk tends to be higher in countries where smoking air-cured, or black, tobacco is more common. At least five studies in Spain, Italy, France, Uruguay, and Argentina have found higher risk among smokers of black tobacco compared with that among smokers of blond tobacco (2, 6, 8, 9, 11).

Bladder cancer risk tends to increase with both increasing duration and increasing intensity of smoking (3, 6, 10, 12-19). Studies that have examined the effect of smoking cessation have shown that bladder cancer risk tends to decrease with increasing time since quitting smoking (2, 3, 6, 10, 13, 14, 17, 19-21). Some have reported that cigarette smokers who inhale deeply may have a greater risk than those who do not (2, 5, 13, 22-24), whereas others have found no association between inhalation and bladder cancer risk (3, 14, 25, 26). There is some evidence to suggest that environmental tobacco smoke (ETS) may increase the risk of bladder cancer in nonsmokers (24). Mutagens found in tobacco smoke have been detected in the blood and urine of nonsmokers (27, 28). Only four epidemiologic studies to date have examined the effect of ETS on bladder cancer, and only one has reported a positive association (13, 24, 29, 30).

The purpose of our study is to examine the risk of bladder cancer in relation to various aspects of cigarette smoking, including the dose response, type of tobacco smoked, smoking cessation, depth of inhalation, and effect of passive smoking among nonsmokers. Bladder cancer occurs primarily in men, with a male-to-female ratio of ~4:1 in most western countries (1, 31). We also estimate the attributable risk for smoking in men and women to determine the proportion of the male excess of bladder cancer that is attributable to cigarette smoking.

Materials and Methods

Cases and controls were selected from 18 hospitals in the following regions of Spain: Barcelona, Valles, Asturias,

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Alicante, and Tenerife. Cases were all male and female patients with newly diagnosed, transitional cell carcinoma of the bladder (*International Classification of Diseases, Ninth Edition* code 1880-1889) or carcinoma *in situ* (*International Classification of Diseases, Ninth Edition* code 2337) of the bladder, including uretric orafice and urachus, who were 21 to 80 years old at the time of diagnosis and resided in the catchment areas of the 18 participating hospitals. Patients who had a previous diagnosis of cancer of the lower urinary tract (i.e., bladder, renal pelvis, ureters, or urethra) were not eligible for study, as were patients with bladder tumors that were secondary to other malignancies. This study was approved by the National Cancer Institute Institutional Review Board, as well as the ethics committees of all participating hospitals. The study began in June 1998 and concluded in September 2000.

We identified 1,453 cases and interviewed 1,219 (84%) of them (1,067 men, 152 women). For each bladder cancer case, one control was selected and individually matched to the case on age (within 5 years), gender, race/ethnicity, and hospital. We identified 1,442 eligible controls and interviewed 1,271 (88%) of them (1,105 men, 166 women). Controls were selected from patients admitted to the same hospital around the same time as the cases for diseases/conditions unrelated to smoking (36% hernias, 12% other abdominal surgery, 12% hydrocele, 24% fractures, 6% other orthopedics, 4% circulatory diseases, 1% ophthalmology diseases, 2% dermatology diseases, and 4% other diagnosis).

Because there were only six non-White subjects included in this study, our analyses are based exclusively on Whites. We also excluded 13 subjects who provided unsatisfactory information on smoking. An additional 257 cases and 235 controls were missing detailed smoking information and are excluded from analyses of smoking intensity, tobacco type, and inhalation. Because only 39 women reported ever smoked cigarettes, the detailed analyses of smoking characteristics were restricted to men.

All subjects were interviewed in the hospital using a computer-assisted personal interview. Before the interview, written informed consent to participate in the study was obtained from each subject. The questionnaire was designed to elicit detailed information on smoking habits, dietary factors, fluid intake, medical conditions, occupational and residential histories, family history of cancer, and history of medication use (i.e., analgesics and nonsteroidal anti-inflammatory drugs). An extensive list of tobacco brands marketed in Spain during the past few decades was used to facilitate recall of smoking information. Each tobacco brand was categorized according to type of tobacco (black versus blond).

Never smokers were defined as subjects who replied ''no'' when asked, ''During your entire lifetime, have you ever smoked a total of ≥100 cigarettes?'' Subjects were defined as occasional smokers if they replied yes to the question above but replied ''no'' when asked if they ever smoked cigarettes regularly, at least one per day for ≥6 months. Information about smoking duration and intensity was not collected from occasional smokers. Regular smokers were defined as subjects who replied ''yes'' to both questions mentioned above. Regular smokers were asked about their smoking habits in detail, including age at which they started or stopped smoking, number of years and usual amount smoked, brands of cigarettes smoked and whether they were made with black or blond tobacco, and depth of inhalation. Subjects were defined as former smokers if the age at which they quit smoking was at least 1 year before the date of interview. Those who reported quitting during the year before the interview were included with current smokers. Pack-years were calculated as follows: (number of cigarettes smoked per day / 20) * (number of years smoked).

We assessed exposure to ETS among nonsmokers by asking them to report the number of persons who smoked around them at every residence and every job held as part of a complete residential and occupational history. We computed a series of exposure metrics to examine bladder cancer risk

Table 1. ORs and 95% CIs for smoking status and type of tobacco smoked

	Males		Females	
	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
Smoking status				
Never smoked	55/227	1.0	106/140	1.0
Occasional smokers †	35/84	1.7 (1.0-2.8)	16/13	1.4 (0.6-3.6)
Ever (regular) smokers	950/782	5.1 (3.7-7.0)	27/12	3.3 (1.3-8.0)
		$P < 0.0001$		$P = 0.007$
Never smoked	55/227	1.0	106/140	1.0
Former smokers	453/464	3.8 (2.8-5.3)	6/6	1.8 (0.5-7.2)
Current smokers ‡	492/314	7.4 (5.3-10.4)	21/6	5.1 (1.6-16.4)
		$P < 0.0001$		$P = 0.005$
Tobacco type				
Never smoked	55/227	1.0	106/140	1.0
Blond tobacco only	86/118	3.2 (2.1-4.8)	9/7	1.6 (0.4-6.0)
Black tobacco only	391/302	5.3 (3.8-7.4)	5/2	3.8 (0.4-38.3)
Both	283/206	6.0 (4.2-8.5)	7/1	—
		$P < 0.0001$		
Black tobacco only				
Never smoked	55/227	1.0	106/140	1.0
Former smokers	211/194	4.2 (2.9-6.0)	0/1	—
Current smokers ‡	176/107	7.3 (4.9-10.9)	5/1	—
		$P < 0.0001$		
Blond tobacco only				
Never smoked	55/227	1.0	106/140	1.0
Former smokers	26/63	1.8 (1.0-3.2)	3/3	—
Current smokers ‡	60/54	5.8 (3.4-10.0)	6/4	—
		$P < 0.0001$		

*Adjusted for age, hospital region, fruit/vegetable consumption, and high-risk occupation.
†An *occasional* smoker is one who reported smoking at least ≥100 cigarettes during his lifetime but who did not smoke regularly (at least one cigarette per day for ≥6 months). No further information was available for occasional smokers, and they are excluded from all subsequent analyses.
‡Subjects were defined as current smokers if the year they quit smoking was within 1 year of the interview.

Table 2. Number of cases and controls, ORs and 95% CIs for bladder cancer according to duration smoked and number of cigarettes smoked per day

	Males			Females	
	Cases/controls	OR* (95% CI)		Cases/controls	OR* (95% CI)
Duration smoked (y)					
Never smoked	55/227	1.0	Never smoked	106/140	1.0
<20	35/79	1.8 (1.1-3.0)	<30	13/10	2.0 (0.6-6.1)
20-29	95/141	2.8 (1.8-4.1)	≥30	13/2	7.2 (1.4-37.1)
30-39	214/202	4.4 (3.1-6.4)			P = 0.009
40-49	287/189	6.5 (4.6-9.3)			
≥50	298/146	8.9 (6.2-12.9)			
		P < 0.0001			
Cigarettes smoked per day					
Never smoked	57/227	1.0	Never smoked	106/140	1.0
1-19	247/275	3.5 (2.5-5.0)	1-19	10/5	3.0 (0.8-10.6)
20-39	530/340	6.8 (4.9-9.5)	≥20	15/7	3.7 (1.1-12.3)
≥40	168/156	4.8 (3.3-6.9)			P = 0.035
		P < 0.0001			
Pack-years					
Tertiles			Median		
Never smoked	55/227	1.0	Never smoked	106/140	1.0
0-25	171/255	2.8 (1.9-3.9)	1-14	7/7	1.8 (0.5-7.0)
25-51	368/259	6.2 (4.4-8.6)	>14	17/5	4.4 (1.3-15.4)
>51	385/235	7.1 (5.0-10.0)			P = 0.02
		P < 0.0001			

*Adjusted for age, hospital region, fruit/vegetable consumption, and high-risk occupation.

associated with ETS exposure in the home and in the workplace among nonsmokers (32). We first computed the total duration that each nonsmoker spent living with one or more smokers as a child (≤18 years old) and as an adult. We then multiplied the duration spent at each residence by the number of smokers in that residence and summed these totals to derive a measure of cumulative residential ETS exposure as a child and as an adult. We computed similar metrics for cumulative occupational ETS exposure by first computing the total duration that each subject spent working around one or more smokers and then multiplying the duration spent at each job by the number of smokers reported for each job.

To estimate the effects of smoking characteristics on bladder cancer risk, we calculated odds ratios (OR) and 95% confidence intervals (95% CI) using unconditional logistic regression, with terms entered for exposure and potential confounding variables (i.e., age at interview, geographic region, employment in a high-risk occupation for bladder cancer, and fruit and vegetable consumption). To test for linear trend, we computed the Wald statistic, treating the exposure variable as a continuous variable by entering the median value for each level of the categorical variable among control subjects. To test for interaction between two risk factors, we added a cross-product term to the logistic model and conducted a likelihood ratio test.

Lastly, we computed population attributable risks (PAR) to examine the proportion of the male excess in bladder cancer risk attributable to smoking, the proportion of bladder cancer due to current versus former smoking, and the proportion of bladder cancer due to smoking black tobacco. Sex-specific PARs were computed using the method of Bruzzi et al. (33) and adjusted for the following potential confounding factors: age at interview, geographic region, and employment in a high-risk occupation for bladder cancer. Based on data from the IARC, we computed age-standardized bladder cancer incidence rates for men and women in the general geographic areas included in our study, weighted by the population in each area (34). The PARs from our study were applied to these incidence rates to quantify the bladder cancer incidence among men and women attributable to cigarette smoking in our study regions.

Results

Among men, current (OR, 7.4; 95% CI, 5.3-10.4) and former (OR, 3.8; 95% CI, 2.8-5.3) smokers had significantly increased risks of bladder cancer compared with never smokers (Table 1). We also observed a marginally significant elevated risk among occasional smokers (those who smoked at least 100 cigarettes in their lifetimes but never smoked regularly; OR, 1.7; 95% CI, 1.0-2.8). About 68% of male smokers reported smoking cigarettes made with black tobacco. Relative to never smokers, risk was higher for men who smoked only black

Table 3. ORs and 95% CIs for duration smoked and number of cigarettes smoked per day, men only

Duration smoked (y)	Cigarettes per day (cases/controls)			Total*
	<20	20 to <40	≥40	
<20	2.0 (1.0-3.9) 16/35	2.6 (1.3-5.3) 16/25	0.2 (0.03-1.7) 1/18	1.3 (0.8-2.3) 33/78
20-29	2.2 (1.3-3.8) 28/51	3.1 (1.9-5.1) 45/62	3.4 (1.8-6.5) 22/28	2.0 (1.3-3.1) 95/141
30-39	2.0 (1.2-3.3) 34/71	7.0 (4.7-10.6) 137/85	4.2 (2.5-7.1) 43/44	3.2 (2.1-4.7) 214/200
40-49	4.0 (2.5-6.5) 60/61	8.5 (5.7-12.6) 169/86	6.6 (3.9-10.9) 58/40	4.6 (3.1-6.8) 287/187
≥50	8.5 (5.3-13.6) 100/48	9.3 (6.1-14.1) 155/73	8.2 (4.4-15.1) 41/22	6.4 (4.3-9.5) 296/143
Total †	1.3 (0.8-2.3) 238/266	1.7 (1.0-3.1) 522/331	2.4 (1.4-4.1) 165/152	

NOTE: ORs relative to never smokers (55 cases, 227 controls), adjusted for age, hospital region, fruit/vegetable consumption, and high-risk occupation.
*Duration smoked adjusted for intensity smoked and relative to never smokers (P_{trend} < 0.0001).
†Intensity smoked adjusted for duration smoked and relative to never smokers (P_{trend} = 0.05).

Table 4. ORs and 95% CIs for duration smoked black tobacco and duration smoked blond tobacco, men only

Duration smoked black tobacco (y)	Duration smoked blond tobacco (y), cases/controls			
	Never smoked	<20	20-29	≥30
Never smoked	1.0 (—) 55/227	1.6 (0.7-4.0) 8/23	1.6 (0.7-3.3) 11/32	5.7 (3.4-9.6) 52/43
<20	2.0 (0.9-4.2) 12/25	3.8 (2.4-6.2) 52/59	8.6 (4.3-17.4) 29/16	7.9 (4.0-15.7) 30/18
20-29	3.6 (2.1-6.3) 39/42	5.1 (2.9-9.2) 36/31	3.5 (1.2-10.5) 6/9	— (—) 5/0
≥30	6.0 (4.2-8.6) 265/180	10.3 (5.5-19.2) 45/19	— (—) 0/1	— (—) 1/1

NOTE: Adjusted for age, hospital region, fruit/vegetable consumption, and high-risk occupation.

tobacco (OR, 5.3; 95% CI, 3.8-7.4) than for men who smoked only blond tobacco (OR, 3.2; 95% CI, 2.1-4.8) and highest for smokers of both types (OR, 6.0; 95% CI, 4.2-8.5). When examining bladder cancer risk associated with smoking status stratified by tobacco type, risk for both former and current smokers was higher for smokers of black tobacco (former: OR, 4.2; 95% CI, 2.9-6.0; current: OR, 7.3; 95% CI, 4.9-10.9) than for those of blond tobacco (former: OR, 1.8; 95% CI, 1.0-3.2; current: OR, 5.8; 95% CI, 3.4-10.0).

Among women, current smokers had an OR (95% CI) of 5.1 (1.6-16.4) and former smokers had an OR (95% CI) of 1.8 (0.5-7.2) compared with never smokers. Risk was slightly elevated among occasional smokers (OR, 1.4; 95% CI, 0.6-3.6), although this elevation was not significant. Few women in our study ever smoked any form of cigarettes (27 cases, 12 controls), and only 12 female cases and 3 female controls reported smoking cigarettes made from black tobacco. As seen among men, risk was higher for women who smoked only black tobacco (OR, 3.8; 95% CI, 0.4-38.3) than for those who smoked only blond tobacco (OR, 1.6; 95% CI, 0.4-6.0) relative to never smokers. There were only 5 cases and 2 controls who smoked black tobacco, however. No systematic differences in smoking-related risk were apparent between genders.

A significant trend in risk with increasing duration smoked was observed for both men and women, with risk peaking at an OR (95% CI) of 8.9 (6.2-12.9) for men who smoked at least 50 years and at an OR (95% CI) of 7.2 (1.4-37.1) for women who smoked at least 30 years (Table 2). The trend in risk by amount smoked (cigarettes per day) was significant, but not consistent, with risk peaking for smokers of one to less than two packs per day but decreasing for smokers of two or more packs per day. When intensity and duration were combined into pack-years, a significant trend of increasing risk associated with increasing pack-years was observed for both men and women.

Table 3 shows risk cross-classified by both duration and intensity smoked relative to risk among nonsmokers (men only). We observed a significant trend in risk with increasing duration adjusted for intensity ($P_{trend} < 0.0001$) as well as a positive gradient in risk within each level of intensity. A consistent trend in risk was also seen with increasing intensity adjusted for duration ($P_{trend} = 0.05$), but the pattern was not consistent within each level of duration. Because the trend in risk was more consistent for duration smoked than for intensity smoked, we examined the effect of tobacco type by duration smoked (Table 4). Long-term smokers were more likely to have smoked only one type of tobacco, and risk tended to be higher for smokers of black tobacco than smokers of blond tobacco at comparable levels of duration. We also examined the risk of smoking only black tobacco relative to smoking only blond tobacco after adjustment for duration smoked; risk for bladder cancer was only 40% higher for smokers of black tobacco compared with smokers of blond tobacco (OR, 1.4; 95% CI, 0.98-2.0).

Table 5 shows the effect of time since quitting by tobacco type smoked. After adjustment for duration smoked, we observed an overall reduction in risk for subjects who had quit smoking within 4 years before the interview and a leveling in risk for those who stopped smoking ≥5 years before the interview. When we restricted the analysis to subjects who smoked only black tobacco, there was no consistent trend in risk with increasing years since quitting. For smokers of blond tobacco, however, a significant inverse trend in risk with increasing time since quitting was apparent ($P = 0.001$). Smokers of blond tobacco who quit ≥20 years before the interview had an OR (95% CI) of 0.2 (0.1-0.9) compared with risk in current smokers of blond tobacco. The interaction between cessation and tobacco type was not significant, however ($P = 0.39$).

Subjects were asked to report whether they typically inhaled into the mouth only, into the throat, or into the chest. Compared with men who inhaled into the mouth only, risk was increased for those who inhaled into the chest (OR, 1.5; 95% CI, 1.1-2.1) as well as for those who inhaled into the throat (OR, 1.7; 95% CI, 1.1-2.6; data not shown). When we stratified risk by inhalation and duration smoked, we observed significant trends of increasing risk with increasing number of years smoked among both subjects who inhaled into the mouth ($P < 0.0001$) and those who inhaled into the throat or chest ($P < 0.0001$; data not shown in tables). In addition, the magnitude of risk was higher for subjects who inhaled into the throat or chest compared with those who inhaled only into the mouth at each level of duration. Compared with nonsmokers, subjects who smoked for ≥50 years and inhaled into the mouth had an OR (95% CI) of 4.8 (2.3-9.9) and those who smoked for ≥50 years and inhaled into the throat or chest had an OR (95% CI) of 10.0 (6.7-15.0) compared with nonsmokers.

Table 5. ORs and 95% CIs for male smokers according to years since quitting, men only

Years since quitting	Cases/controls	OR (95% CI)
All smokers		
Current smokers*	394/254	1.0
2-4	54/50	0.6 (0.4-1.0)
5-9	85/54	1.0 (0.7-1.5)
10-19	126/137	0.7 (0.5-1.0)
≥20	85/116	0.8 (0.5-1.3)
		$P = 0.24$
Black tobacco smokers only †		
Current smokers*	172/105	1.0
2-4	26/20	0.8 (0.4-1.5)
5-9	42/27	0.9 (0.5-1.6)
10-19	78/72	0.9 (0.5-1.5)
≥20	62/72	0.6 (0.3-1.2)
		$P = 0.79$
Blond tobacco smokers only †		
Current smokers*	59/53	1.0
2-4	5/8	0.5 (0.1-1.8)
5-9	7/9	0.7 (0.2-2.2)
10-19	10/24	0.2 (0.04-0.6)
≥20	3/20	0.2 (0.1-0.9)
		$P = 0.001$

NOTE: Adjusted for age, hospital region, duration smoked, fruit/vegetable consumption, and high-risk occupation.
*Subjects were defined as current smokers if the year they quit smoking was within 1 year of the interview, adjusted for tobacco type.
†Smokers of both black and blond tobacco were excluded.

Table 6. ORs and 95% CIs for cumulative residential and occupational exposure to ETS among nonsmokers

ETS exposure	Males		Females	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Childhood residential*				
No exposure	28/124	1.0	49/49	1.0
<18 y	21/74	1.2 (0.6-2.3)	42/71	0.7 (0.3-1.4)
18 y	6/26	0.9 (0.3-2.6)	14/17	0.6 (0.2-1.7)
		$P = 0.92$		$P = 0.24$
Adult residential†				
No exposure	24/106	1.0	34/38	1.0
>0 to ≤26	13/52	1.1 (0.5-2.4)	21/22	2.2 (0.8-6.2)
>26 to ≤54	7/37	0.8 (0.3-2.2)	28/35	1.9 (0.7-4.8)
>54	10/31	1.3 (0.5-3.2)	23/44	0.8 (0.3-1.9)
		$P = 0.74$		$P = 0.27$
Occupational‡				
No exposure	13/31	1.0	62/97	1.0
>0 to ≤135	14/57	0.6 (0.2-1.6)	18/22	1.7 (0.7-4.0)
>135 to ≤240	9/67	0.2 (0.1-0.7)	13/13	1.7 (0.6-4.4)
>240	19/72	0.6 (0.2-1.4)	13/8	3.3 (1.1-9.5)
		$P = 0.58$		$P = 0.03$

NOTE: Adjusted for age, hospital region, fruit/vegetable consumption, and high-risk occupation.
*Sum of the years spent at each childhood residence (up to age 18 years) multiplied by the number of smokers in each residence and categorized above and below the median value in controls.
†Sum of the years spent at each adult residence multiplied by the number of smokers in each residence and categorized according to tertiles in controls.
‡Sum of the years spent at each job multiplied by the number of smokers at each job and categorized according to tertiles in controls.

Nonsmokers of cigarettes (55 male, 106 female cases; 227 male, 140 female controls) were queried about exposure to ETS at home and at work. We observed no significant association between bladder cancer risk and any overall exposure to ETS (OR, 0.7; 95% CI, 0.3-2.3), in the residence (OR, 2.1; 95% CI, 0.5-8.8), or at work (OR, 0.7; 95% CI, 0.2-2.4). To examine the risk associated with exposure to ETS in more detail, we computed separate risk estimates for cumulative residential ETS exposure during childhood (up to 18 years old) and during adulthood as well as occupational ETS exposure (Table 6). None of the residential measures of ETS exposure was associated with bladder cancer risk for either men or women. We did observe a significant trend of increasing risk associated with cumulative occupational ETS exposure in women, but a similar trend was not observed in men.

In our study regions, the male-to-female ratio for incident bladder cancer was 8.2 based on a male standardized incidence rate of 28.0 (3,683 cases) and a female standardized incidence rate of 3.4 (593 cases). To determine the proportion of the male excess that may be due to cigarette smoking, we calculated the attributable risk for bladder cancer associated with cigarette smoking for men (PAR, 0.75) and women (PAR, 0.14) based on data from our study. We then applied these PARs to the incidence rates in men and women to estimate the number of incident cases due to cigarette smoking. After subtracting the number of cases due to smoking, we recomputed the sex ratio with the cases due to smoking removed. The sex ratio decreased from 8.2 to 1.7 after the effect of cigarette smoking was eliminated.

To examine the proportion of bladder cancer incidence in our study regions that could be prevented if current smokers were to quit smoking, we computed the PARs for former and current smoking. Of the total attributable risk for bladder cancer associated with cigarette smoking among men, the proportion associated with current smoking was 0.42 and that associated with former smoking was 0.33. Among women, the proportion associated with current smoking was 0.13, whereas that associated with former smoking was 0.02. For men, we also computed the PARs for bladder cancer associated with smoking blond tobacco only (0.06), black tobacco only (0.31), both blond and black tobacco (0.24), and unknown type (0.15). The number of women who ever smoked black tobacco ($n = 15$) was too small to compute PARs for type of tobacco smoked.

Discussion

Smoking-related bladder cancer risks in our study were higher than those observed in other case-control studies, suggesting that smoking is a strong risk factor for bladder cancer in Spain. These high risks possibly explain, in part, the high incidence of bladder cancer in Spain compared with most other industrialized countries. We found that former and current smokers experienced risks of bladder cancer three to seven times higher than nonsmokers, respectively. We also observed elevated risks for bladder cancer among men and women with very low levels of consumption, or those we classified as occasional smokers. Because we did not collect detailed smoking information from occasional smokers, we were unable to further explore this association. It is possible, however, that true risk may have been underestimated in previous studies where subjects with similar low levels of consumption were classified as never smokers.

For both men and women, we observed significant positive trends in risk with both increasing duration and intensity smoked. A regular duration-response relationship has been observed in most studies that investigated the issue (3, 6, 10, 12-19). Bladder cancer risk also tends to increase with increasing intensity of smoking. However, the shape of the dose-response curve has varied across studies, with some reporting little change in risk from moderate to heavy smoking levels (3, 6, 16-19, 35-37), which is consistent with our findings. The plateauing of the dose-response curve may be because heavy smokers may inhale proportionately less than light smokers, causing a leveling off of exposure. When we examined intensity stratified by level of inhalation, the does-response curve for intensity still plateaued within each strata of inhalation, making this explanation unlikely. Alternatively, variation in the genetic factors that affect carcinogen activation, detoxification, or saturation of key metabolic activation processes may occur at high levels of tobacco exposure (31).

This is the largest study to date to evaluate the effects of black versus blond tobacco use. We found that smokers of black tobacco tended to have higher risks than smokers of blond tobacco at comparable levels of duration smoked. However, risk for bladder cancer was only 40% higher for smokers of black tobacco compared with smokers of blond tobacco, and this elevation was not statistically significant. Our findings suggest

that risk associated with black tobacco compared with blond tobacco may not be as high as reported in previous studies, which have suggested that smokers of black tobacco have one and one-half to three times the risk of smokers of blond tobacco (2, 6, 8-11). In an earlier case-control study conducted in Spain (including the region of Barcelona), Lopez-Abente et al. (5) reported little to no difference in bladder cancer risk associated with tobacco type. In this study, as in our study, tobacco type was classified based on smokers of one type or the other, exclusively. In contrast, other studies have classified tobacco type based on the total proportion of lifetime cigarette use (i.e., >50% of lifetime cigarette use was black tobacco), thereby mixing together smokers of both tobacco types (2, 9).

Several carcinogens may be responsible for the increased bladder cancer risk experienced by smokers, and laboratory evidence suggests that aromatic amines play a prominent role (38). Black tobacco has higher concentrations of *N*-nitrosamine and 2-napthylamine than blond tobacco (10). In addition, blood levels of 4-aminobiphenyl and adducts of several other aromatic amines are higher for smokers of black tobacco than of blond tobacco (39). Lastly, urine mutagenicity is higher among smokers of black tobacco (27, 28).

We observed a significant inverse trend in risk with increasing time since quitting for smokers of blond tobacco, but not among smokers of black tobacco, although the interaction between cessation and tobacco type was not significant. Only two previous studies (2, 10) examined the effect of quitting smoking cigarettes made with black tobacco. In both studies, a decreasing risk with increasing years since quitting was observed. However, black tobacco smokers were mixed with blond tobacco smokers in both studies. In our study, black and blond tobacco smokers were categorized according to the type of tobacco they smoked exclusively.

For smokers of blond tobacco, our findings suggest that risk among those who stopped smoking for many years approximates that of nonsmokers, which is consistent with several previous studies (6, 14, 17, 20, 21). Findings from other studies, however, indicate that a reduction in risk occurs within the first 2 to 4 years after stopping but that risk either does not continue to decline with increasing time since quitting (3, 10, 13, 19) or continues to decline but does not return to the level of nonsmokers even after 25 years of cessation (12). It has been suggested that the almost immediate effect of cessation of blond tobacco observed in some studies indicates the presence of late-stage carcinogens, the effects of which are not apparent with cessation of black tobacco. If replicated in other studies, these finding may provide additional mechanistic insight into the effects of tobacco type and cessation.

Smokers who inhale deeply may have a greater risk than those who do not (2, 5, 13, 22, 24). Some previous studies reported no association between bladder cancer risk and inhalation (3, 14, 25, 26). Our findings suggest that those who inhale past the mouth, into the throat or chest, have a 50% to 70% increased risk compared with those who inhale into the mouth. We saw little difference in risk, however, between those who inhaled into the throat versus the chest. Inconsistencies in risk observed for the effect of inhalation are likely due to differences in ascertainment and subjective assessments of inhalation (2, 5, 13, 23).

Although we observed no association between bladder cancer risk and any type of ETS exposure overall among nonsmokers, we did see a significant trend of increasing risk associated with increasing cumulative occupational ETS exposure among female nonsmokers, but not among male nonsmokers. This trend in risk with occupational ETS exposure among women may be due to chance because no pattern of risk with residential ETS exposure was apparent in either women or men. However, it is possible that the reference group among women is a pure group composed of women truly unexposed to ETS, whereas several men who reported no exposure may in fact have received exposure to ETS in the workplace. We found that 66% of the 159 women who reported no occupational ETS exposure also reported being housewives and therefore were more likely to have had absolutely no occupational exposure to ETS. Given the high prevalence of smoking among men in Spain, it is unclear if men who reported no occupational ETS exposure were truly unexposed. If there is less misclassification of exposure among women, then the observed trend in risk among women may be less biased than that observed among men. Four studies have evaluated the association between ETS and bladder cancer, and only one showed increasing risks with increasing number of years of ETS exposure (13, 24, 29, 30). In several other studies that examined cancer (40) or other diseases, such as asthma (41), a stronger effect was observed for exposures to ETS at work than in the residence. More research is needed to determine if ETS exposure is a cause of bladder cancer.

The male-to-female ratio for bladder cancer incidence was 8.2 in our study areas, which is considerably higher than the sex ratios reported in most previous studies (31). Some have speculated that the high sex ratios observed in some countries may be due to the large differences in smoking prevalence between men and women (42). To test this hypothesis, we removed the number of incident cases due to smoking in men and women from the incidence rates in our study areas. The sex ratio fell from 8.2 to 1.7, suggesting that the high sex ratio may be largely due to smoking, although the contribution of additional factors cannot be ruled out. Two factors contribute to the higher PAR for smoking in men than in women. First, the prevalence of smoking in our study was higher among men (37%) compared with women (8.7%). Second, the point estimates for smoking tended to be higher in men (OR, 7.4 current; OR, 3.8 former) than women (OR, 5.1 current; OR, 1.8 former), although these differences were not significant. In addition, nondifferential misclassification of cigarette smoking in our study may have led to underestimation of the true risk of bladder cancer associated with cigarette smoking. If this occurred, the sex ratio after the removal of the effect of smoking may, in fact, be substantially lower than 1.7, suggesting that smoking explains almost the entire male excess of bladder cancer in Spain. This observation contrasts with that of Hartge et al. (43), who found that cigarette smoking and occupational exposures explained only a part of the male excess of bladder cancer in the United States.

The PARs computed for current and former smokers suggest that in Spain 42% of bladder cancer occurring in men and 13% in women could be prevented if current smokers were to quit smoking. We also computed the PARs for type of tobacco smoked. Among men, the proportion of bladder cancers associated with smoking black tobacco exclusively was 31% and that associated with smoking both blond and black tobacco was 24%, indicating that 55% of bladder cancers among Spanish men may be explained by use of black tobacco.

In summary, cigarette smoking is a strong risk factor for bladder cancer in Spain. We observed significant trends in risk with increasing duration and intensity smoked for both men and women. The dose-response was more pronounced for duration than intensity smoked. Among men, risk for black tobacco smokers was consistently higher than that for blond tobacco smokers at comparable levels of duration. However, these differences were not significant and black tobacco smokers had only a 40% higher risk than blond tobacco smokers, which is not as high as reported previously. Reductions in risk associated with quitting smoking may be more pronounced for smokers of blond tobacco compared with smokers of black tobacco. Deep inhalation, into the throat or chest, may confer higher risk than inhalation into the mouth only. Residential ETS exposure among nonsmokers did not seem to increase risk, although occupational ETS exposure in female nonsmokers did confer some risk and deserves further

attention. Finally, nearly the entire male excess in bladder cancer observed in countries with high sex ratios (i.e., 6:1 to 9:1), such as Spain and other countries in southern Europe,[1] may be explained by the higher prevalence of smoking among men compared with women, rather than by occupational/environmental exposures to other bladder carcinogens.

Appendix A. Participating Study Centers in Spain

Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, Barcelona-Coordinating Center (M. Kogevinas, N. Malats, F.X. Real, M. Sala, G. Castaño, M. Torà, D. Puente, C. Villanueva, C. Murta, J. Fortuny, E. López, S. Hernández, and R. Jaramillo); Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona (J. Lloreta, S. Serrano, L. Ferrer, A. Gelabert, J. Carles, O. Bielsa, and K. Villadiego), Hospital Germans Tries i Pujol, Badalona, Barcelona (L. Cecchini, J.M. Saladié, and L. Ibarz); Hospital de Sant Boi, Sant Boi, Barcelona (M. Céspedes); Centre Hospitalari Parc Taulí, Sabadell, Barcelona (C. Serra, D. García, J. Pujadas, R. Hernando, A. Cabezuelo, C. Abad, A. Prera, and J. Prat); Centre Hospitalari i Cardiològic, Manresa, Barcelona (M. Domènech, J. Badal, and J. Malet); Hospital Universitario, La Laguna, Tenerife (R. García-Closas, J. Rodríguez de Vera, and A.I. Martín); Hospital La Candelaria, Santa Cruz, Tenerife (J. Taño and F. Cáceres); Hospital General Universitario de Elche, Universidad Miguel Hernández, Elche, Alicante (A. Carrato, F. García-López, M. Ull, A. Teruel, E. Andrada, A. Bustos, A. Castillejo, and J.L. Soto); Universidad de Oviedo, Oviedo, Asturias (A. Tardón); Hospital San Agustín, Avilés, Asturias (J.L. Guate, J.M. Lanzas, and J. Velasco); Hospital Central Covadonga, Oviedo, Asturias (J.M. Fernández, J.J. Rodríguez, and A. Herrero), Hospital Central General, Oviedo, Asturias (R. Abascal, C. Manzano, and T. Miralles); Hospital de Cabueñes, Gijón, Asturias (M. Rivas and M. Arguelles); Hospital de Jove, Gijón, Asturias (M. Díaz, J. Sánchez, and O. González); Hospital de Cruz Roja, Gijón, Asturias (A. Mateos, V. Frade); Hospital Alvarez-Buylla, Mieres, Asturias (P. Muntañola and C. Pravia); Hospital Jarrio, Coaña, Asturias (A.M. Huescar and F. Huergo); and Hospital Carmen y Severo Ochoa, Cangas, Asturias (J. Mosquera).

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