Tobacco consumption and bladder cancer in non-coffee drinkers

G López-Abente, A Escolar

Tobacco consumption is the principal known risk factor for urinary bladder cancer. This relation has been analytically characterised on the basis of different aspects of the smoking habit (inhalation pattern, tobacco type, duration).[1][2] Other risk factors described for bladder cancer are occupation and coffee consumption,[1][3–5] although results for coffee consumption have been contradictory. The important role of cigarette smoking as a confounding factor has been one of the traditional difficulties hindering research into the association between coffee consumption and bladder cancer. In general, studies that have restricted analysis to non-smokers show a weak positive association for coffee consumption, with no effect observed among the smoker stratum. This latter finding is indicative that coffee drinking could have an "attenuator" effect on the risk associated with tobacco use.

In this report, we present the results of a new analysis of the association between cigarette smoking and bladder cancer, in which coffee drinkers were separated from non-coffee drinkers, an aspect that, to our knowledge, has never been published until now.

Methods

Data came from a multicentre case-control study, the design and results of which have been published elsewhere.[2][5] In short, all new cases of bladder cancer diagnosed in the period, January 1985 to March 1986 (incident cases) and all those diagnosed in the period, 1983–1984 (prevalent cases), were included. Cases were selected from 12 general hospitals spread throughout five Spanish provinces (Barcelona, Madrid, Cádiz, Guipúzcoa and Vizcaya) and totalled 497 histologically confirmed cases of carcinoma, polyps and papilloma of the bladder, occurring in men and women under age 80 years at diagnosis and resident in the province where the hospital was located. Two controls (hospital and popula-

tion), matched by sex and age (± 5 years), were included for each case, making a total of 583 hospital and 530 population controls.

Interviews were carried out at subjects' homes by trained interviewers who had not been informed as to interviewee case/control status. The questionnaire contained sections dealing with occupational history, tobacco use, passive exposure to tobacco smoke, diet, coffee consumption, use of artificial sweeteners, consumption of analgesics and past history of diabetes, lithiasis and urinary infections. In the section dealing with tobacco use, a complete history was obtained on cigarette, cigar and pipe tobacco consumption, by profiling levels of consumption, tobacco brand, type and characteristics (black, blond, filter and low tar) and duration of all periods in which use occurred.[2][5] Non-coffee drinkers were defined as those drinking fewer than two cups a week. A logistic regression analysis was run to estimate the odds ratio (OR) for each variable. All risk estimates shown have been adjusted for age, sex and place of residence.

Results

Table 1 sets out the distribution of controls with respect to cigarette and coffee consumption. From this distribution, it will be seen that cigarette and coffee consumption are closely linked, proving very similar in both types of controls.

In table 2, estimation of the effect of cigarette smoking is shown separately for the two constituent coffee consumption strata. Among non-coffee drinkers, 30 cases (91%) were smokers, while among controls the figure was 58%. The effect of cigarette smoking on bladder cancer risk was systematically estimated to be more than double among non-coffee drinkers than among coffee drinkers. The plateau in the effect of smoking over 10 cigarettes/day observed in the initial analysis[2] was maintained in both strata, as was the dose response effect

Cancer Epidemiology Unit, National Centre for Epidemiology, Carlos III Institute of Health, Madrid, Spain
G López-Abente

Hospital Universitario "Puerta del Mar", Servicio de Medicina Preventiva y Salud Pública, Cádiz, Spain
A Escolar

Correspondence to:
Dr López-Abente, Servicio de Epidemiología del Cáncer, Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Sinesio Delgado, 6, 28029 Madrid, Spain (glabente@isciii.es)

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Table 1   *Distribution of hospital and population controls by smoking habit and coffee consumption*

| | Total | Non-smoker | Ex-smoker | Current smokers (cigarettes/day) | | | |
				1–10	11–20	21–30	31+
Coffee drinkers							
Hospital controls*	393	60 (15.3)†	85 (21.7)	49 (12.5)	135 (34.4)	46 (11.8)	16 (4.1)
Population controls*	386	63 (16.4)	107 (27.9)	51 (13.3)	111 (28.9)	40 (10.4)	12 (3.1)
Ex-coffee drinkers							
Hospital controls	41	10 (24.4)	17 (41.5)	4 (9.8)	8 (19.5)	1 (2.4)	1 (2.4)
Population controls	43	12 (27.9)	16 (37.2)	4 (9.3)	7 (16.3)	4 (9.3)	0 (0.0)
Non-coffee drinkers							
Hospital controls‡	57	24 (44.4)	16 (29.6)	8 (14.8)	4 (7.4)	1 (1.9)	1 (1.9)
Population controls	43	17 (39.5)	12 (27.9)	3 (7.0)	7 (16.3)	2 (4.7)	2 (4.7)

*Data were missing for two hospital controls and two population controls. †Numbers in parentheses are percentages. ‡Data were missing for three hospital controls.

Table 2 Odds ratios of bladder cancer in male coffee and non-coffee drinkers by cigarette consumption (compared with non-smokers)

Coffee drinkers				Non-coffee drinkers			
Variable	Cases	Controls	OR	95% CI	Variable	Cases	Controls	OR	95% CI
Tobacco					*Tobacco*				
Non-smoker	24	123	1	Reference	Non-smoker	3	41	1	Reference
Smoker	337	655	2.71	1.71, 4.31	Smoker	30	57	7.31	2.05, 26.11
Non-smoker	24	123	1	Reference	Non-smoker	3	41	1	Reference
Ex-smoker	69	192	1.96	1.16, 3.31	Ex-smoker	6	28	3.08	0.68, 13.98
Current smoker	268	463	3.03	1.89, 4.84	Current smoker	24	29	11.72	3.06, 44.87
Cigarettes/day					*Cigarettes/day*				
among smokers in general					among smokers in general				
0	24	123	1	Reference	0	3	41	1	Reference
1–10	33	180	1.46	0.85, 2.53	1–10	3	27	1.33	0.24, 7.32
11–20	206	323	3.40	2.11, 5.48	11–20	20	19	20.09	4.85, 83.18
21–30	58	111	2.80	1.62, 4.85	>20	7	9	10.57	2.07, 54.09
≥31	22	38	2.87	1.44, 5.75					
Cigarettes/day					*Cigarettes/day*				
among current smokers					among current smokers				
0	24	123	1	Reference	0	3	41	1	Reference
1–10	33	100	1.75	0.96, 3.17	1–10	3	11	2.89	0.47, 17.69
11–20	173	246	3.81	2.33, 6.22	11–20	16	11	34.76	6.70, 180.26
21–30	46	86	2.97	1.67, 5.31	>20	5	6	10.37	1.65, 65.09
≥31	15	28	2.84	1.31, 6.19					
Years of smoking					*Years of smoking*				
0	24	123	1	Reference	0	3	41	1	Reference
1–19	23	60	1.85	0.96, 3.57	1–30	3	10	3.44	0.57, 20.60
20–39	109	235	2.23	1.34, 3.69	>30	27	47	8.38	2.30, 30.55
40–59	192	333	3.30	2.30, 5.37					
≥60	13	27	3.09	1.36, 7.05					
Cigarettes/lifetime					*Cigarettes/lifetime*				
0	24	123	1	Reference	0	3	41	1	Reference
<150.000	61	199	1.60	0.94, 2.71	<150.000	5	25	2.09	0.44, 10.02
150–299.999	149	262	3.03	1.85, 4.94	150–299.999	17	18	18.60	4.36, 79.40
≥300.000	125	191	3.62	2.19, 5.98	≥300.000	8	12	11.87	2.35, 59.89

Non-coffee drinkers exclude ex-coffee drinkers.

for the duration of the habit. The results are similar when the two control groups (hospital and population) are analysed separately.

Discussion

The results suggest that the relative risk of suffering bladder cancer among cigarette smokers who do not drink coffee may be far higher than that published so far and that exposure to coffee may thus have an "attenuator"' effect on the risk associated with tobacco use. None the less, odds ratios of about 3 were also seen for smoking among coffee drinkers.

Studying non-coffee drinkers by strata is difficult in that the two habits are closely linked, and there is a paucity of cases at the reference level (that is, never smokers). This leads to lack of precision in the estimations. The risk none the less remains very high when a reference level is established composed of non-smokers and ex-smokers.

The role of caffeine in somatic damage induced by carcinogenic agents has been the subject of several studies. In vitro studies indicate that caffeine may have a booster effect on the cytotoxic effect of certain compounds[6] (for example, DNA intercalating agents). In addition results have been published that point to the role of coffee consumption as effect modifier of other exposures on the risk of cancers with *ras* mutations.[7] In contrast, other studies discuss its possible protective effect, by acting as an antimutagenic through formation of complex compounds.[8–10] All authors are however unanimous when it comes to establishing its influence on DNA repair and damage mechanisms. Furthermore, the toxicity of caffeine seems to be lower among smokers.[11]

Caffeine moreover reduces the number of mutations induced in vitro by a carcinogenic aromatic amine (MeIQx), possibly because of an alteration of the spectrum of enzymes involved in its activation.[12] Among these enzymes is cytochrome P4501A2 (CYP1A2). Caffeine acts as an inductor of CYP1A2 activity, which may be related to risk of bladder cancer through metabolic activation of aromatic amines and formation of compounds that in turn lead to formation of DNA adducts.[13] High consumption of coffee (more than four cups of coffee per day)[13] has been observed to lead to such induction in N-oxidation activity, dependent—among other factors—on CYP1A2.

Recently published results suggest the presence of complex modifying effects phenomenon of the cigarette smoking and coffee consumption in colon cancer[14] and between alcohol and coffee consumption in liver cancer.[15] In addition, studies in laboratory animals have shown a protector effect of the caffeine in rats treated with nicotine derived carcinogens[16] and the inhibition of the cell proliferation and metastatic behaviour of melanoma cancer cells.[17]

The results of our study suggest that the risk of suffering bladder cancer among cigarette smokers may be far higher than that published to date, and that coffee consumption exercises a modulating role, affording a certain protection against the carcinogenic risk associated with smoking. It would be of great interest to evaluate CYP1A2 and acetilisation phenotype activity, along with possible coffee induced modification of tobacco related effects, in future studies on bladder cancer and studies on any other tumour sites that have considered both risk factors.

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