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Relative importance of risk factors in bladder carcinogenesis: some new results about Mediterranean habits

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In the Mediterranean region of France where bladder cancer mortality and incidence are high, a case-control study with 219 male incident cases and 794 randomized, male population-controls was carried out in 1987-89 to investigate bladder cancer risk factors and more specifically, regional factors. A stepwise logistic regression was applied to the data. This investigation confirms the role of tobacco and of certain occupational exposures in bladder carcinogenesis. There was a significant dose-response relationship with lifelong coffee drinking and alcohol consumption; however the risk estimates were only significantly elevated for the heaviest drinkers. The intake of saccharin was not associated with risk of bladder cancer. Infrequent consumption of carrots, spinach, and marrows conferred an increased risk, suggesting a protective effect of vitamin A. Finally, this investigation results in some new hypotheses. The study of residences and birthplaces has revealed a lower risk for those who have lived in a non-Mediterranean area and a higher risk for those born in a Mediterranean area. These features might be explained by some Mediterranean dietary habits, such as a high consumption of spices (odds ratio = 3.64, 95 percent confidence interval = 2.21-5.98). *Cancer Causes and Control* 1994, **5**, 326 - 332

Key words: Alcohol, β-carotene, bladder cancer, case-control study, coffee, France, males, spices, Mediterranean habits, smoking.

Introduction

In the Hérault region of France, near the Mediterranean coast, the bladder cancer mortality rates are higher than those in other French areas: the standard mortality ratio is 1.35 ($P < 0.01$).[1] According to the Hérault Cancer Registry, the bladder cancer annual incidence rate standardized on the world population (24.8/100,000)[2] is the highest in France, the range of the annual incidence rates provided by seven other French registries being 13.8/100,000 in the Tarn area to 22.8/100,000 in the Bas-Rhin area. A case-control study with 219 male incident cases and 794 male population controls was carried out in 1987-89 in order to investigate bladder cancer risk factors, and more specifically regional factors, and to rate them.

The present paper shows the hierarchy of the different risk factors using a stepwise logistic regression

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model. These findings are discussed according to their original features in comparison with literature.

Materials and methods

Case and control selection

Since the sex ratio for bladder cancer is about 1:4 with a higher incidence among men,[2] only a male sample was studied.

The cases included in the study consisted of all the French newly-diagnosed cases who had been living in the Hérault district for more than five years, and who were diagnosed with a primary, histologically confirmed, bladder carcinoma between January 1987 and May 1989. Polyps/papillomas were excluded in order to ensure a more homogeneous population. The Hérault Cancer Registry was used to check and to complete the lists of cases identified by urologists.

Controls were randomly selected from electoral rolls in the whole of the Hérault region. In order to maximize similarity with the cases, only men over the age of 50 years who had been living in the Hérault area for more than five years were included.

Data collection

Cases were questioned by two closely supervised interviewers who also contacted and questioned population controls listed in the telephone directory. Controls not listed in the directory (nonsubscribers or ex-directory) were sent a letter, a questionnaire, and a stamped addressed envelope.

The interview (an average of 25 min) used a structured and rigidly formatted questionnaire. Trained interviewers obtained information on demography (birthplace, different places of residence, level of education) and occupational exposures; all jobs with a duration of at least one year were registered. The smoking history was expressed as cigarette-equivalents: a cigarillo equalled one cigarette-equivalent, and a pipe 2.5 cigarette-equivalents. There were no cigar smokers in our sample.

The dietary habits studied included the consumption of coffee, tea, and alcohol, expressed as the quantity of pure alcohol ingested by men from the different alcoholic beverages (wine, beer, aperitif, spirits). The intake of artificial sweeteners dealt with the use of saccharin as a food additive only, and the consumption of saccharin from other sources (food and drink) was not considered.

The starting age, degree (subject-reported numbers), duration, and possible changes of each exposure were registered in order to estimate the lifetime cumulative individual exposure.

Finally, subjects were questioned about dietary habits, such as their spice consumption: foods not spiced; moderately spiced (with some pepper); and highly spiced (with anise, curry powder, ginger, mustard, paprika, peppers, pimento, or mixed spice such as harissa). They were also asked in fixed frequency categories (never, less than once a week, more than once a week) about their consumption of vegetables such as carrots, Brussels sprouts, cauliflower, French beans, leeks, marrows (squash), spinach, and tomatoes.

Response rate

A total of 219 of the 272 cases identified were interviewed; the remaining 53 had died. Among the controls listed in the directory, 558 of 692 (80.6 percent) agreed to be interviewed. Among the controls not listed in the directory, 236 of 329 (71.7 percent) answered by mail; 227 controls did not answer (22.2 percent); 161 (16.7 percent) could not be found (death, change of address); and 66 (6.5 percent) refused for the following reasons: old age (11; 16.7 percent), disease or handicap (11, 16.7 percent), opposition to sampling principle (8, 12.1 percent), or no interest (36, 54.5 percent).

Statistical analysis

This was performed using the BMDP Statistical Software (Berkely, CA, USA) package. The collected information was compared, first between controls listed and not listed in the directory, and second between cases and controls using a one-way analysis of variance for quantitative variables and a χ^2 test for qualitative variables.

The effects of the different factors on bladder cancer risk were measured by the odds ratio (OR) estimated by the method of maximum likelihood from a multiple logistic regression.[3] Ninety-five percent confidence intervals (CI) were based on the standard error of coefficient estimates and normal approximation. The analysis was performed by a step-by-step inclusion of the strongest independent variables selected among those variables which showed a significant influence on the risk of bladder cancer when considered alone.

Results

No differences in responses were found between controls interviewed and those responding by mail (Table 1); thus they were analyzed together.

Cases were significantly older than controls. They did not differ from controls in education level or marital status; most of them had had a primary education and were married. Their lifelong consumption of tobacco, coffee, and alcohol was significantly higher

Table 1. Bladder cancer case-control study (France—Hérault 1987-89): features of the surveyed sample according to case and control status

Variables	Cases (n = 219)	Controls	
		Not in directory (n = 236)	In directory (n = 556)
Mean age (yrs)	67.8	64.6	65.5
Smokers (%)[a]	88.6	67.8	67.0
Average lifelong smoking (cigarette-equivalents)	353,554	264,890	246,919
Coffee drinkers (%)[b]	93.2	87.7	88.0
Average lifelong coffee drinking (cups)	58,882	43,174	39,194
Alcohol drinkers (%)[c]	91.3	86.0	85.8
Average lifelong alcohol drinking (g pure alcohol)	1,084,800	827,233	807,313
Saccharin users (%)	13.7	7.2	6.3
Average lifelong saccharin intake (tablets)	1,834	2,845	2,106
Occupation at risk for bladder cancer (%)			
Oil refinery workers	1.8	0.0	0.2
Mechanics	8.7	6.8	4.0
Drivers	11.0	7.2	7.6
Dyers	1.8	0.4	0.4
Plumbers	4.1	2.1	1.3
Cooks	2.7	0.0	0.7
Residence in a non-Mediterranean area (%)	26.9	40.7	36.4
Birthplace in a Mediterranean area (%)	40.6	42.9	40.6
Consumption of carrots, spinach, marrows less than once a week (%)	25.3	12.7	17.2
High spices consumption (%)	30.0	14.5	12.1

[a] A smoker is defined as an individual who has smoked at least one cigarette-equivalent per day for a continuous period of one year or more. A cigarillo is equal to 1 cigarette-equivalent, and a pipe to 2.5 cigarette-equivalents.
[b] A coffee drinker is an individual who has drunk at least one cup of any type of coffee per day for a continuous period of one year or more.
[c] An alcohol drinker is an individual who has drunk at least 15,000 g of pure alcohol for a continuous period of 1 year or more.

than that of controls; there was no significant difference in their lifelong intake of saccharin. The only significant differences in professions between cases and controls concerned the following occupations: oil refinery workers, mechanics, drivers, dyers, plumbers, and cooks. Vegetable consumption did not differ between cases and controls except for carrots, spinach, and marrows which were eaten significantly less often by cases (less than once a week). Significantly more cases than controls had consumed highly-spiced foods. More controls than cases had lived in a non-Mediterranean area of France (*i.e.*, other than Provence-Alpes-Côte d'Azur, Languedoc-Roussillon, and Corsica). With regard to birthplaces in 'Mediterranean areas' (Provence-Alpes-Côte d'Azur, Languedoc-Roussillon, Corsica, Italy, Spain, North Africa), there was no significant difference.

Table 2 shows the most important bladder cancer risk factors ranked according to increasing log-likelihood in the step-by-step process: lifelong tobacco-smoking, coffee-drinking, spice consumption, age, high risk occupation for bladder cancer, residence in a non-Mediterranean area, consumption of carrots, spinach, and marrows less than once a week, lifelong alcohol-drinking, birthplace in a Mediterranean area.

The bladder cancer risk increased with age. The results for lifelong tobacco-smoking, coffee-drinking, and alcohol consumption show a highly significant dose-response relationship which was confirmed when these variables were treated as continuous in the logistic regression model. Finally, the role of some regional characteristics must be highlighted: eating spicy dishes and being born in a Mediterranean area increased the risk, whereas having lived in a non-Mediterranean district reduced the risk. The use of saccharin was not statistically associated with bladder cancer risk.

Smokers of black tobacco had a slightly increased risk of bladder cancer relative to smokers of blond tobacco (adjusted OR = 1.6, CI = 0.7-3.6). Compared with non-coffee drinkers, those who drank more than seven cups of any type of coffee per week for a continuous period of one year or more had an adjusted bladder-cancer OR of 1.6 (CI = 0.8-3.2). The adjusted OR corresponding to ground regular, instant regular, ground decaffeinated, and instant decaffeinated coffee were respectively: 1.4 (CI = 0.8-2.7), 0.6 (CI = 0.2-1.6), 0.3 (CI = 0.1-1.6), and 0.4 (CI = 0.1-1.6).

Table 2. Bladder cancer case-control study (France—Hérault 1987-89): relative importance of risk factors according to the stepwise logistic regression[a]

	Cases	Controls	OR	(CI)[b]
Lifelong tobacco smoking (cigarette-equivalents)				
< 365	11	217	1.0	
365-146,000	31	181	3.4	(1.6-7.8)
146,001-320,000	43	156	5.0	(2.4-10.7)
> 320,000	76	131	8.7	(4.2-17.8)
Lifelong coffee-drinking (cups)				
< 365	8	79	1.0	
365-25,000	36	212	1.6	(0.6-3.8)
25,001-60,000	59	296	1.6	(0.6-3.8)
> 60,000	58	98	4.1	(1.7-10.0)
Spice consumption				
No	114	601	1.0	
Yes	47	84	3.6	(2.2-6.0)
Age (yrs)				
< 55	8	102	1.0	
55-64	46	239	2.0	(0.9-4.7)
65-74	64	231	3.2	(1.4-7.3)
⩾ 75	43	113	5.5	(2.3-13.4)
Occupation at risk for bladder cancer				
No	115	595	1.0	
Yes	46	94	2.5	(1.5-4.0)
Residence in a non-Mediterranean area				
No	121	431	1.0	
Yes	40	254	0.4	(0.2-0.7)
Infrequent consumption of carrots, spinach, marrows				
No	42	110	1.0	
Yes	119	575	1.7	(1.1-2.8)
Lifelong alcohol-drinking (g of pure alcohol)				
< 15,000	7	63	1.0	
15,000-600,000	47	246	2.2	(0.9-5.6)
600,001-1,200,000	57	259	1.7	(0.7-4.3)
> 1,200,000	50	121	3.1	(1.2-8.2)
Birthplace in a Mediterranean area				
No	94	402	1.0	
Yes	67	283	1.6	(1.0-2.7)
Saccharin intake				
< 365	140	641	1.0	
⩾ 365	21	44	1.5	(0.8-3.0)

[a] The largest possible data set was used in the logistic regression model, *i.e.*, the set of persons having no missing values for any of the model variables.

[b] (CI) = 95% confidence interval.

Discussion

Results are discussed according to their original features and three categories considered: conclusions already known, responses to questions already examined in the literature but which led to contradictory issues, and conclusions that result in new hypotheses.

This study corroborates certain results previously described in the epidemiology of bladder cancer. This pathology particularly affects older men, and its incidence increases with age.[4,5] The role of smoking is undeniable; the dose-response relationship was highly significant for lifelong tobacco-smoking. The adjusted ORs of bladder cancer are among the highest figures published so far.[6-23] In other Mediterranean countries such as Italy,[20-22] Spain,[9-10] and Greece,[19] the ORs are also higher than those observed in the United States and the United Kingdom. This difference could be due to the type of tobacco smoked. Black tobacco appears to be twice carcinogenic as blond tobacco.[12,20] It is used quite commonly in Mediterranean countries and relatively uncommonly elsewhere. Among smokers in this French study, 93.6 percent of cases and 86.2 percent of controls used predominantly black tobacco (> 50 percent of lifelong tobacco use). This hypothesis is consistent with experimental data suggesting that black

tobacco is more carcinogenic than blond tobacco. Indeed, urinary mutagenicity and levels of 4-aminobiphenyl (a potent human bladder carcinogen) hemoglobin adducts were higher in smokers of black tobacco than of blond tobacco.[24-25] Aromatic amines and nitrosamines are more concentrated in black than blond tobacco smoke.[21] However, our data do not fully demonstrate that use of black tobacco itself confers increased risk of bladder cancer since the point estimate of the OR for black- *cf* blond-tobacco users, although greater than one, did not reach statistical significance. But our study lacks power to show such an association.

Some occupations are reported in the literature to be associated with bladder cancer risk: the risks for all refinery workers,[11,18,26,27] mechanics,[11,26,27-32] drivers,[27,30,33,34] dyers,[35,36] and cooks[11,27,30,37] were confirmed in this investigation. Nevertheless, the small sizes of each occupational group do not allow the effect upon risk of duration of exposure or starting age to be studied.

The consistency of all these results with findings published by most authors can be regarded as a validation of our data.

This study also tried to answer some other questions already examined in the literature but which led to contradictory issues. Results relative to coffee drinking are consistent with results from earlier epidemiologic studies, many of which report slightly and inconsistently elevated risks of bladder cancer among coffee drinkers.[11,16,38-44] In their meta-analysis, Viscoli *et al*[45] also concluded that "the best available data do not suggest a clinically important association between the regular use of coffee and development of cancer of the lower urinary tract in men or women." However, in our investigation, a clear dose-response relationship was found between life-long coffee drinking and risk of bladder cancer. Only Escolar Pujolar *et al*,[46] and Marrett *et al*[47] examined this factor. Marrett *et al*[47] described a pattern similar to ours. As underlined by Viscoli *et al*,[45] there is a substantial variation between findings concerning coffee drinking and cancer of the bladder. This disparity might be explained by the type of coffee, but most authors[16,38-41] disregard this variable. In our study, most drinkers (82.3 percent) used ground regular (nondecaffeinated) coffee, whereas instant coffee is predominant in other countries such as the UK.[43] The role of coffee in bladder carcinogenesis could depend on the type of coffee; in the present investigation, only drinkers of regular ground coffee have bladder cancer ORs higher than one. The other drinkers did not seem to be at risk for bladder cancer, but the small numbers of subjects in these categories do not allow firm conclusions to be drawn. Finally, our findings are consistent with the existence of a relationship between coffee drinking and risk of bladder cancer. However, in spite of the inclusion of tobacco-smoking and other correlates of coffee in the model, the coffee-drinking effect may still be confounded because of its high correlation with its correlates. Unfortunately, there are too few nonsmokers to perform analyses in this group.

Findings relative to overall alcohol intake reveal that the risk of bladder cancer depends on the amount of alcohol consumed. The risk is only applicable to those whose drinking is at the high end of the population distribution. In spite of their large sample of cases and controls, Thomas *et al*[48] did not find a consistent relationship regarding the amount of alcoholic drink servings per week; neither did Bravo *et al*.[49] However, they did not obtain information on lifelong consumption—their interviewers only asked about the amount drunk during a typical week in the previous winter. Under-reporting of alcohol consumption probably occurred; indeed, there is less drinking among older groups, and since their sample was predominantly elderly, former drinkers might have responded as if they were abstainers or light drinkers, biasing the results toward the null findings. If we used the same methods as these authors, we would also fail to show a significant dose-response relationship since there were many cases who had progressively reduced their alcohol intake: 40 percent among wine drinkers, 17 percent among beer drinkers, 26 percent among 'pastis' drinkers (pastis is a local aperitif with anise), and 10 percent among spirit drinkers.

The intake of saccharin is not found to be associated with the risk of bladder cancer, in accordance with most previous results,[42,50-52] except those of Howe *et al*.[53]

Despite using simple dietary questions, this study showed increased risk conferred by infrequent (less than once a week) consumption of carrots, spinach, and marrows. These three vegetables are rich in β-carotene. Mettlin and Graham,[54] who determined an index of vitamin A intake from 22 foods, have observed that the gender-adjusted risks of bladder cancer associated with the three lowest levels of vitamin A intake relative to the highest level are significantly elevated. Risch *et al*,[42] Kolonel *et al*,[55] and Paganini-Hill[56] do not give any statistically significant results. The difficulties of precisely measuring nutrition retrospectively show the need for caution when interpreting these findings. Nevertheless, based on its role in regulating cell differentiation in epithelia,[57] the hypothesized protective role of vitamin A in bladder carcinogenesis is biologically plausible. Moreover, an effect of β-carotene itself, independent of vitamin A, cannot be excluded.[58]

This investigation has led to some new assumptions.

The study of residences and of birthplaces has revealed a lower bladder cancer risk for those who lived in a non-Mediterranean area of France and a higher risk for those who were born near the Mediterranean coast, whether it be in France or in another Mediterranean country (*e.g.*, Spain, Italy, North Africa). This geographic distribution of the pathology suggests the role of some regional customs, such as diet, in bladder carcinogenesis.

One factor contributing to the development of bladder cancer might be the consumption of spices, which is very common in all Mediterranean countries, especially in Morocco, Tunisia, and Algeria. According to local physicians, bladder cancer incidence could be high in these countries, but there is no tumor registry to obtain estimates of these incidence rates.

After the Algerian war, in 1962, most French nationals who lived in this country came back and settled in the south of France, near the Mediterranean coast and more particularly in the Hérault area. They represent 17 percent of the surveyed population, and it is likely that they retained their dietary habits, including a consumption of spicy food. In this study, eating highly spicy dishes is statistically associated with bladder cancer risk. To the best of our knowledge, no author has reported such a result. Nevertheless, it is conceivable that spices may irritate and consequently modify the bladder epithelium. This hypothesis deserves further investigation, with a thorough study of spice consumption, including type, frequency of intake, and quantity.

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