

Bladder Cancer in Relation to Cigarette Smoking¹

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ABSTRACT

The importance of smoking-related variables in the development of bladder cancer was examined in data from a hospital-based case-control study of 1316 male and 505 female cases, and 3940 male and 1504 female age-matched controls interviewed in 20 hospitals from 9 United States cities between 1969 and 1984.

For male current smokers, odds ratios for number of cigarettes smoked per day (cpd) increased to approximately 2.5 for smokers of more than 20 cpd, after adjustment for duration and nonsmoking-related covariates. Above 20 cpd, no further increase in odds ratio was observed. In females, the adjusted odds ratios showed no significant effect of increasing cpd level. In males, the odds ratios for duration increased from 1.18 (0.52-2.72) in those who smoked for less than 20 years to 2.31 (1.65-3.24) in those who smoked for greater than 40 years. In females, the corresponding odds ratios were 0.97 (0.27-3.44) and 1.62 (1.00-2.62). The results did not suggest an increased risk with early age at start of smoking in either sex. Ex-cigarette smokers, as a whole, had reduced odds ratios for bladder cancer, but the extent of the reduction was similar in short-term and longer-term quitters.

The findings of this investigation support an association between smoking and bladder cancer. The pattern of risk associated with cpd and duration among current smokers and the early decline in risk associated with quitting are discussed in relation to possible mechanisms of bladder carcinogenesis.

INTRODUCTION

Changes in bladder cancer incidence rates over the past 45 years differ from those of lung cancer, which show an abrupt rise following, by approximately 20 years, the dramatic increase in cigarette consumption which began after World War I and ended in the 1970s (1). Since 1940, United States male bladder cancer incidence rates have increased, although less strikingly than lung cancer rates. Incidence rates among white males (around 20 per 100,000 in 1970) have consistently been more than twice those of nonwhite males (1). The incidence rates in females have declined slightly and continue to be lower than those of males. Rates among white females, however, have been higher than those among nonwhite females (around 6.0 versus 4.0 per 100,000 in 1970). Despite the differences between lung cancer and bladder cancer incidence, numerous retrospective studies (2) have corroborated the association between cigarette smoking and bladder cancer in both sexes. Risk ratios for smokers compared to never-smokers average between 2.0 and 4.0. The association is clearly not as strong as that for cancers of the lung, oral cavity, or larynx. In spite of apparently lower attributable risks, cigarette smoking is a major etiological factor affecting bladder cancer rates in countries of high cigarette smoking prevalence, such as the United States.

Using data from a large hospital-based case-control study, we investigated the importance of smoking-related variables, including cpd,³ duration, age at start, and time since quitting smoking.

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³ The abbreviation used is: cpd, cigarettes smoked per day.

METHODS

The cases and controls used in this study were interviewed between 1969 and 1984 in 20 hospitals located in 9 United States cities as part of a large hospital-based study of smoking-related cancers. The original study of tobacco-related cancers has been described in previous publications (3, 4). Briefly, patients diagnosed with smoking-related cancers and controls were identified by interviewers in collaborating hospitals in each of the cities according to the study protocol. Only histologically confirmed diagnoses of primary cancer which had been made within the year preceding interview were eligible as cases for the study. Until 1979, diagnosis within 5 years was allowed, but less than 15% of cases were diagnosed more than 1 year prior to interview. Cases and controls had to be 20-85 years old and not too ill to be interviewed. Controls were hospitalized patients with an admitting diagnosis consisting of conditions not thought to be related to smoking and diagnosed within the year preceding interview. The exclusion of smoking-related conditions from control diagnoses was intended to reduce potential bias in the assessment of risks due to cigarette smoking. Controls were time matched to cases within 2 months of interview. About 11% of the eligible cases and 7% of controls refused to be interviewed.

Here, we categorized exposure to cigarettes as follows: never-smokers, current smokers, and ex-cigarette smokers. Never-smokers were defined as those who had never smoked as much as one cigarette, cigar, or pipe a day for a period of 1 year. A current smoker was defined as someone who had smoked cigarettes only for a continuous period of 1 year or more and was also smoking within the year preceding diagnosis. Ex-cigarette smokers were defined as those who had smoked cigarettes exclusively in the past but who had quit smoking for over 1 year at the time of diagnosis. Cigar and pipe smokers were excluded from analysis.

Controls were frequency-matched to cases by age (± 5 years) and sex (5). Frequency matching involved first determining the number of male and female cases in each age category and then randomly selecting up to three controls per case from the control pool in order to fill the quota for each age category. Where there were fewer than three eligible controls per case, all available controls were included in the data set.

Using a structured questionnaire, trained interviewers obtained information on demographic as well as smoking-related variables. The age at which the subject began smoking, number of years of smoking, and average number of cpd for different brands were obtained from current and ex-cigarette smokers. Ex-cigarette smokers were also asked about the number of years since they quit smoking.

In a previous report based on the same data (6), we observed similar risks for nonfilter cigarette smokers and those who had switched from nonfilter to filter cigarettes, but a slightly reduced risk for exclusively filter cigarette smokers. Therefore, in this study, we decided to combine nonfilter cigarette smokers and nonfilter to filter switchers to examine the effect of smoking-related variables.

Odds ratios were computed in two ways. We derived OR_a , which is the odds ratio based on the comparison of the factor without accounting for other covariates. We also computed OR_b from the logistic regression model (7), which was obtained by fitting $k - 1$ dummy variables representing k levels of the variable of interest, while simultaneously accounting for pertinent covariates. Those variables which showed a significant effect when considered alone, for either sex, were included as covariates in the logistic regression analysis.

To determine whether there was a reduction in risk conferred by quitting smoking, ex-cigarette smokers were compared to current cigarette smokers as the referent category. Since certain time-related variables were linear combinations of one another, *e.g.*, among ex-cigarette smokers, age at diagnosis = age at starting plus duration of smoking plus time since quitting, we controlled for only two time-related variables in the equation, while looking at the effect of time since quitting.

RESULTS

Demographic Variables. The distribution of cases and controls by age, education, marital status, religion, and occupation is presented in Table 1. No significant differences between cases and controls were found for any of the demographic variables examined. A broad classification by occupational status did not show any association with bladder cancer in men or women. Specific analysis for selected high-risk occupations, including chemical workers, machinists, printers, and truck-, bus-, and taxi-drivers, also did not show any case-control differences.

Smoking-related Variables. Table 2 presents the mean age at diagnosis, age at start of smoking, duration, and cpd among current and ex-smokers for cases and controls. Despite matching for age, cases were older than controls among female never-smokers and current smokers ($P < 0.05$), and among male ex-smokers ($P < 0.005$). Among male never-smokers, cases were slightly younger than controls ($P < 0.05$). In both sexes, among current as well as ex-smokers, cases smoked for more years than controls and the differences were statistically significant ($P < 0.05$). For male current and ex-smokers, cases had higher mean cpd than controls ($P < 0.005$). Mean years since quitting was shorter among male cases than controls ($P < 0.005$).

Table 3 presents the unadjusted and multivariable-adjusted

Table 1 Distribution of demographic variables among cases and controls^a

	Males		Females	
	Cases (N = 1316) (%)	Controls (N = 3940) (%)	Cases (N = 505) (%)	Controls (N = 1504) (%)
Age				
<44	4.9	4.9	5.9	6.0
45-54	18.2	18.3	13.9	14.0
55-64	37.6	37.7	30.9	31.1
65-74	32.2	32.3	34.9	35.1
75+	7.0	6.8	14.5	13.8
Education				
None, grammar school	21.1	24.7	22.0	22.7
Some high school	19.9	16.7	24.8	17.4
High school graduate	22.4	24.0	30.3	30.5
Some college	13.6	11.2	12.8	15.4
College	11.6	10.8	6.0	8.5
Postgraduate	11.4	12.8	4.2	5.5
Marital status				
Single	5.4	8.3	11.2	8.4
Married	80.7	74.1	46.7	54.0
Divorced	5.1	7.3	6.2	5.8
Separated	2.7	3.2	3.0	1.9
Widowed	6.0	7.1	32.9	29.9
Religious status				
Protestant	37.5	39.1	39.8	39.1
Catholic	38.6	35.6	38.1	35.6
Jewish	18.9	20.3	18.1	21.7
Other	3.1	3.0	2.0	2.8
None	1.8	2.0	2.0	0.9
Race				
Caucasian	91.7	86.7	88.1	90.4
Black	6.8	11.1	9.5	8.3
Hispanic	0.5	1.0	2.2	1.1
Oriental	0.6	0.4	0.0	0.1
Other	0.3	0.8	0.2	0.1
Occupation				
Professional	14.9	15.6	7.4	7.5
Business executive	10.5	11.1	2.2	3.2
Technical	9.2	7.5	14.3	17.0
Clerical/sales	16.0	14.4	7.4	7.2
Skilled	16.5	14.4	7.4	6.6
Semiskilled	7.7	8.2	1.6	2.6
Unskilled	4.4	6.3	4.8	2.6
Retired/unemployed	20.8	22.3	13.1	13.3
Housewife			42.0	40.1

^a Includes never-smokers and all current smokers and ex-smokers regardless of filter status.

Table 2 Mean age at diagnosis, age at start, duration, cigarettes/day, and years since quitting, by smoking status

	Never-smokers		Current smokers		Ex-smokers	
	Cases	Controls	Cases	Controls	Cases	Controls
Males						
Total no.	192	1207	673	1376	390	1121
Age at diagnosis (yr)	60.2 ^a	62.4	59.9	59.4	64.6 ^b	62.9
Age at start of smoking (yr)			17.2	17.7	17.6	18.1
Duration of smoking (yr)			42.3 ^a	41.2	32.9 ^b	28.7
Cigarettes/day			27.1 ^b	25.2	33.1 ^b	28.5
Yr since quitting smoking					14.0 ^b	15.8
Females						
Total no.	208	898	183	283	65	205
Age at diagnosis (yr)	66.6 ^a	64.9	61.2 ^a	59.5	63.9	63.2
Age at start of smoking (yr)			20.5	21.3	21.4	21.5
Duration of smoking (yr)			40.6 ^b	37.9	31.5 ^a	28.1
Cigarettes/day			22.3	20.3	20.6	19.8
Yr since quitting smoking					10.8	13.1

^a Case-control difference significant at $P < 0.05$.

^b Case-control difference significant at $P < 0.005$.

Table 3 Odds ratios with 95% confidence intervals for different cpd levels among current smokers relative to never-smokers

Cigarettes/day	95% confidence intervals			95% confidence intervals
	Cases	Controls	OR _a	
Males				
Never	192	1207	1.00	1.00
1-10	69	224	1.94	1.43-2.63
11-20	293	611	3.01	2.46-3.68
21-30	121	201	3.78	2.92-4.91
31+	190	340	3.51	2.80-4.41
Females				
Never	208	898	1.00	1.00
1-10	32	88	1.57	1.02-2.41
11-20	94	118	3.44	2.55-4.64
21-30	32	38	3.64	2.28-5.80
31+	24	39	2.66	1.59-4.44

^a OR_a, unadjusted odds ratio; OR_b, adjusted for duration (25-35 years, 35-45 years, 45+ years versus never plus <25 years); education (12-17 years and 17+ years versus <12 years); race (whites versus others), and marital status (married versus others).

odds ratios for different cigarette exposure levels (cpd) for current smokers relative to never-smokers. In both sexes, the odds ratios, adjusted only for nonsmoking-related covariates (age, education, race, and marital status) were similar in magnitude to the unadjusted odds ratios and remained significant in all but the 1-10 cpd group in females (data not shown). After accounting for education, race, marital status, and duration of smoking, the adjusted odds ratios were decreased compared to the unadjusted, especially in females. In males, the odds ratios were statistically significant in the three highest cpd categories, the highest being observed in the 21-30 cpd group. In females, there was no significant effect for cpd at any level after accounting for duration, education, race, and marital status. Results presented exclude age from the logistic model in order to avoid the instability of regression coefficients that might result from the high correlation between age and smoking duration (among current smokers, the correlations were $r = 0.81$; $P < 0.001$ in males and $r = 0.65$; $P < 0.001$ in females). Subsequent inclusion of age in the model, however, did not materially alter these results (data not shown).

Shown in Table 4 are the odds ratios for different durations of smoking. Adjustments for just age, education, race, and marital status did not alter the magnitude of the crude odds ratios (data not shown). Adjustment for cpd, in addition to the

Table 4 Odds ratios with 95% confidence intervals for different durations among current smokers relative to never-smokers

Duration (yr)	Cases	Con- trols	OR _a ^a	95% con- fidence intervals	OR _b	95% con- fidence intervals
Males						
0 (never smoked)	192	1207	1.00		1.00	
<20	6	21	1.80	0.72–4.45	1.18	0.52–2.72
21–30	73	181	2.54	1.87–3.44	1.60	1.03–2.49
31–40	219	434	3.17	2.55–3.94	2.03	1.42–2.90
41+	375	740	3.19	2.63–3.86	2.31	1.65–3.24
Females						
0 (never smoked)	208	898	1.00		1.00	
<20	3	4	3.24	0.78–13.45	0.97	0.27–3.44
21–30	21	58	1.56	0.93–2.62	0.71	0.36–1.41
31–40	63	111	2.45	1.75–3.43	1.13	0.66–1.92
41+	96	107	3.87	2.87–5.23	1.62	1.00–2.62

^aOR_a, unadjusted odds ratio; OR_b, adjusted for cpd (11–20, 21–30, 31+ versus never and <10 cpd); age (continuous variable); education (12–17 years, 17+ years versus <12 years); race (whites versus others); and marital status (married versus others).

Table 5 Effect of years since quitting on risk of bladder cancer for male and female ex-smokers relative to current smokers

Yr since quitting	Cases	Con- trols	OR _a ^a	95% con- fidence intervals	OR _b	95% con- fidence intervals
Males						
0 (current smoker)	673	1376	1.00		1.00	
≤6 yr	107	283	0.77	0.61–0.98	0.71	0.55–0.91
7–12 yr	90	258	0.71	0.55–0.92	0.65	0.49–0.87
≥13 yr	193	580	0.68	0.56–0.82	0.69	0.52–0.91
Overall	390	1121	0.71	0.61–0.82	0.70	0.58–0.84
Females						
0 (current smoker)	183	283	1.00		1.00	
≤6 yr	26	66	0.61	0.37–0.99	0.66	0.40–1.09
7–12 yr	16	57	0.43	0.24–0.77	0.54	0.29–1.02
≥13 yr	23	82	0.43	0.27–0.71	0.65	0.34–1.22
Overall	65	205	0.49	0.35–0.68	0.62	0.42–0.91

^aOR_a, unadjusted odds ratio; OR_b, adjusted for cpd (11–20, 21+ versus 1–10 cpd); duration (31–40 years, 41+ years versus <30 years); age (continuous variable); education (12–17, 17+ versus <12 years); race (whites versus others); marital status (married versus others).

other covariates, reduced the odds ratios substantially. In spite of the correlation of duration with age, the effects of duration were evident in the adjusted odds ratios. The three highest categories in males and the highest category in females had statistically significant odds ratios. A positive gradient was also evident in the odds ratios (test of linear trend, $P < 0.05$). The unadjusted odds ratios for males and females for age at start of smoking suggested an increased risk among those who started smoking early in life, but no trend was discernible after adjustment for duration, cpd, education, race, and marital status (data not shown).

Table 5 shows the effect of quitting smoking, among those who quit for different lengths of time, compared to current smokers. In the logistic model, age was included along with duration of smoking, since the correlation coefficients between age and duration of smoking in ex-smokers ($r < 0.5$) were not as large as in current smokers. In males, there was evidence of significant reduction in risk at all levels, including those who had quit for ≤6 years. The reduction associated with short-term quitting, even as few as ≤6 years, was comparable to that associated with longer time since quitting. In females, there was a similar reduction in risk at all levels. Those who had quit for ≤6 years had similar risk to those who had quit for ≥13 years. We also examined the risk of those who had quit for 12–20 years and greater than 20 years in males, where there were sufficient numbers of cases and controls. This broader categorization did not materially alter the odds ratios which remained at approximately 0.6. In females, the numbers were too small in these categories to permit analysis. Overall, ex-smokers had

an odds ratio of 0.70 (0.58–0.84) in males and 0.62 (0.42–0.91) in females, compared to current smokers.

Although our concern in assessing the effect of quitting dictated a comparison with current smokers, we were also interested in looking at the effect of never smoking. The comparison between those who never smoked versus currently smoking males and females, after adjustments for nonsmoking-related covariates, produced odds ratios of 0.34 (0.28–0.41) and 0.41 (0.32–0.54), respectively.

DISCUSSION

This study is consistent with previous studies suggesting that cigarette smoking is causally associated with cancer of the bladder. For current smokers we have examined the effect due to cpd and duration by mutually adjusting for each other along with other nonsmoking-related covariates. In males, there was a significant effect of cpd. In females, however, the observed effect of cpd in the unadjusted analysis (OR_a), disappeared after adjustment for covariates. When males and females were combined, the effect of cpd was significant ($P < 0.003$) in the upper three levels, after adjustment for covariates including sex, while the effect of duration was significant ($P < 0.001$) only in the upper two levels. Hartge *et al.* (8) have also reported a significant effect of cpd ($P < 0.001$) and borderline significant effect of duration ($P < 0.07$) when both variables were treated as continuous in a regression model. Although an effect of duration has been noted in these two case-control studies, these studies may not adequately assess the effect of duration, since in both studies, controls were frequency-matched to cases on age, which is highly correlated with duration of smoking.

The comparatively lower magnitude of the odds ratio with cpd and duration of smoking in bladder cancer compared to lung cancer suggests a relatively weaker role of cigarettes in bladder cancer. This may be because cigarette smoke has no direct contact with the urinary bladder. Approximately 80% of the “tar” inhaled from mainstream cigarette smoke is deposited in the respiratory tract, the majority in the tracheobronchial region (2). Compounds in tobacco smoke, such as nicotine, or their metabolites, *e.g.*, nitrates and secondary amines, that are thought to be carcinogenic in the bladder, are present in urine in relatively low concentrations (9). Only 10–15% of nicotine in a cigarette is identified in the smoker’s urine 2–3 h after smoking (10). The concentrations of nitrosamines in the urine are low, on the order of 0.01 to 1.00 parts per billion (11).

The risk pattern seen in ex-cigarette smokers is interesting. The reduction in odds ratio is similar in each of the duration of ex-smoking categories, *i.e.*, approximately 0.6–0.7. The extent of the observed reduction in those who quit as few as 6 years prior to diagnosis relative to current smokers is similar to that observed in those who had quit 13 or more years prior to diagnosis. A similar reduction in risk among short-term quitters is also reported by Hartge *et al.* (8). Other studies have examined the effect of years since quitting but without adjusting for duration of smoking (3, 4, 12). The reduction in risk among short-term quitters is consistent with an effect of cigarette smoking occurring at a later stage of bladder carcinogenesis. When the exposure is withdrawn the risk decreases, reaching its maximum reduction in a short time. There appears to be no progressive reduction in risk with increased years since quitting. Nevertheless, ex-cigarette smokers have an elevated odds ratio relative to never-smokers. In a previous report (6), we noted the absence of a reduction in risk among switchers from non-filter to filter cigarettes. These two findings, taken together,

imply that cigarette smoke also exerts an irreversible early-stage effect on bladder carcinogenesis.

The pattern of risk with cpd in our study is curious in that males show a leveling-off of risk after the 20–30 cpd category. This could result from an underreporting of exposure by heavier smokers. We reviewed studies on bladder cancer that have described the cigarette dose-response patterns using cpd categories comparable to those in our study. Several showed a pattern similar to ours (13–15), while others (12, 16–18) showed a continuing increase in the odds ratios across all levels of exposure. Some other studies (3, 4) showed an equivocal pattern. If the leveling-off pattern reflects a real effect, this implies an upper threshold on bladder cancer risk. One way in which such an apparent upper threshold could arise is through a correlation of beverage consumption with smoking. It is known that those who smoke heaviest, say >30 cpd, are likely to be heavy alcohol/coffee drinkers (19). In epidemiological studies neither coffee nor alcohol alone has been consistently shown to affect bladder cancer risk (20–22). It is possible, however, that the diuretic property of these drinks might protect the bladder epithelium from greater concentrations of cigarette-derived carcinogens in the urine (urogenous contact hypothesis). Braver *et al.* (23) have found that greater urine concentration and less frequent micturition augment the risk of bladder cancer.

The reasons for the difference in incidence curves for bladder and lung cancer remain uncertain. The proportion of bladder cancer attributable to smoking is estimated to be about 50% in males and 25% in females (2), implying the presence of other factors in bladder carcinogenesis. Occupational exposures in high-risk industries are thought to account for some cases of bladder cancer (22). Other as yet unidentified etiological factors, possibly dietary in nature, may play a role. One ecological study has demonstrated a correlation of dietary fat intake ($r = 0.7$) with bladder cancer mortality (24). In animals (25), as well as in humans (26), an inverse relationship has been found between vitamin A intake and bladder cancer.

Further studies are required to explore the possible effect of diet on bladder carcinogenesis and the possible synergistic effect of diet- and smoking-related variables on bladder cancer risk.

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