The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies

The Impact of Characteristics of Cigarette Smoking on Urinary Tract Cancer Risk

A Meta-Analysis of Epidemiologic Studies

Maurice P. A. Zeegers, M.Sc.[1]
Frans E. S. Tan, Ph.D.[2]
Elisabeth Dorant, Ph.D., M.D.[1]
Piet A. van den Brandt, Ph.D.[1]

[1] Maastricht University, Department of Epidemiology, Maastricht, The Netherlands.

[2] Maastricht University, Department of Methodology and Statistics, Maastricht, The Netherlands.

Address for reprints: Maurice P. A. Zeegers, M.Sc., Maastricht University, Department of Epidemiology, P.O. Box 616, 6200 MD Maastricht, The Netherlands.

Received November 8, 1999; revision received March 7, 2000; accepted April 3, 2000.

BACKGROUND. Although narrative reviews have concluded that there is strong support for an association between cigarette smoking and urinary tract cancer, the association has never been quantified systematically in reviews. The purpose of this systematic review was to summarize and quantify the impact of different smoking characteristics (status, amount, duration, cessation, and age at first exposure) both unadjusted and adjusted for age and gender.

METHODS. The authors included 43 epidemiologic studies (8 cohort and 35 case–control) and calculated summary odds ratios (SORs) by meta-regression analyses for different smoking characteristics. They also evaluated changes in summary estimates according to differences in study methodology.

RESULTS. Smoking status and increased amount and duration of smoking were associated with a strong increased risk of urinary tract cancer. Smoking cessation and age at first exposure were negatively associated with the risk of urinary tract cancer. The age- and gender-adjusted SORs for current and former cigarette smokers compared with those for nonsmokers were 3.33 (95% confidence interval [CI], 2.63–4.21) and 1.98 (CI, 1.72–2.29), respectively. Even though the component studies differed in methodology, the results were rather consistent.

CONCLUSIONS. The results suggest a substantial increase in risk of cancer of the urinary tract for cigarette smokers. Based on the results of this study and previous literature, the authors conclude that current cigarette smokers have an approximately threefold higher risk of urinary tract cancer than nonsmokers. In Europe, approximately half of urinary tract cancer cases among males and one-third of cases among females might be attributable to cigarette smoking. ***Cancer* 2000;89: 630–9.** *© 2000 American Cancer Society.*

KEYWORDS: cigarette smoking, urologic neoplasms, bladder neoplasms, meta-analysis, epidemiology.

Over the last 4 decades, many epidemiologic studies have been conducted to investigate an association between cigarette smoking and the development of urinary tract cancer. Currently, a substantial amount of evidence has accumulated in support of a positive association between cigarette smoking and urinary tract cancer risk. A positive association has been consistently shown in both men and women in many different geographic areas. Similar results have been obtained in numerous case–control and follow-up studies.

Although cigarette smoking explains the occurrence of a greater amount of urinary tract cancer than does any other known environmental factor (e.g., occupation)[1] and no other environmental factor has been shown to confound this association, to our knowledge no

systematic review on the association between several smoking characteristics and urinary tract cancer has been conducted.

Earlier narrative reviews on cigarette smoking and urinary tract cancer have summarized the association for current cigarette smoking compared with nonsmokers by estimating a general relative risk without calculation or systematic collection of data.[1–9] According to these narrative reviews, typical cigarette smokers have two to four times the risk of nonsmokers. Most narrative reviews suggested that the risk of urinary tract cancer increases with the number of cigarettes regularly smoked.[1,3–11]

The magnitude of the effects of other cigarette smoking characteristics (e.g., smoking duration and cessation or age at first exposure) also has not been systematically reviewed. Although duration of smoking has been evaluated less often than intensity, some narrative reviews reported an unquantified positive dose–response relation.[3,5,6] According to some reviews, former cigarette smokers seem to have a reduced incidence of urinary tract cancer as compared with current smokers.[4–8,11] Age at first exposure to smoking has been reported only occasionally in narrative reviews of cigarette smoking and urinary tract cancer.

The purpose of the current study was to review all epidemiologic studies from 1966 to March 2000 more systematically; to provide quantitative summary estimates of the risk of urinary tract cancer with emphasis on smoking status, duration, amount, cessation, and age at first exposure based on these studies; and to evaluate changes in summary estimates according to differences in study methodology.

METHODS

Search Strategy

The study design has been published previously.[12] Epidemiologic studies were identified through computerized MEDLINE, CANCERLIT, and Current Contents searches for follow-up and case–control studies published until March 2000. The keywords used were urolo*, bladder, cyst*, vesic*, kidney, glomerul*, nephr*, pyel*, renal, ureteral, urethral, transitional cell, cancer, carcino*, tumo*, neoplasm*, onco*, risk, etiology, epidemiology, and caus*. References cited in published original and review articles were examined further. For inclusion in this analysis, the articles had to provide sufficient information to estimate a summary odds ratio and the associated standard error of incident primary urinary tract cancer for at least one of the following cigarette smoking characteristics: cigarette smoking status, average daily cigarette consumption, total duration of cigarette consumption, number of years since cessation, and age at first exposure of smoking. Urinary tract cancer was defined as cancer of the renal pelvis, ureter, urinary bladder, or urethra.

Data Collection

We developed a criteria list for the assessment of quality items (study characteristics) in observational cancer research. This list is used to provide covariables for inclusion in meta-regression models to explore reasons for observed heterogeneity in results between observational studies. The criteria list has been validated on published articles on alcohol intake associated with bladder cancer through consensus meetings with experts on the fields of cancer and meta-analysis. The list calls for the following: general information—year of publication, research design (case–control study, follow-up study, other, unknown), and geographic area (Europe, United States, Asia, Africa, unknown); exposure information—exposure measurement (personal interview, telephone interview, questionnaire, medical records, other, unknown), trained interviewer (yes, no, not applicable [n/a], unknown), validation exposure measurement (yes, no, unknown), and reference period (number of years, lifetime, unknown); case information—source cases (hospital, population, other, unknown), site carcinoma (renal pelvis, ureter, urinary bladder, urethra, urinary tract, unknown), histologic confirmation cases (yes, no, unknown), and percentage transitional cell tumors; case–control study information—source controls (hospital, population, neighborhood, other, n/a, unknown), response rate (percentage, n/a, unknown), and blinding of case status (yes, no, n/a, unknown); follow-up study information—source study population (volunteer, population, other, n/a, unknown), years of follow-up (number of years, n/a, unknown), blinding of exposure status (yes, no, n/a, unknown), and completeness of follow-up (percentage, n/a, unknown).

We extracted data allowing us to calculate both unadjusted and adjusted odds ratios to estimate the association between cigarette smoking and the risk of urinary tract cancer. We constructed two-way contingency tables for each study, based on exposure frequency distributions, to calculate the unadjusted odds ratios. Adjusted odds ratios were extracted directly from the original reports. Because we considered age and gender to be the most important confounding variables, the authors of the original articles had to have adjusted for at least these two variables for inclusion in the calculation of adjusted summary estimates. If studies reported gender-stratified age-adjusted odds ratios, we combined these estimates by

calculating age- and gender-adjusted odds ratios,[13] because from both theoretically and statistically points of view, gender is probably a confounder in the association between cigarette smoking and bladder cancer. For studies that reported separate adjusted odds ratios for several exposure strata, we combined the exposure specific odds ratios by using the prevalence of the noncases as weight.[14] Summary odds ratios were calculated for smoking status (non-, former, and current smoker), smoking amount (0, 1–20, and > 20 cigarettes/day), smoking duration (≤ 20 and > 20 years), smoking cessation (> 10 and ≤ 10 years), and age at first exposure of smoking (20 years and ≤ 20 years). Unfortunately, most component studies did not include simultaneously different smoking characteristics in a regression model to estimate the impact of cigarette smoking status, amount, duration, and age at first exposure solely.

Statistical Analysis

To detect publication or related biases, we explored heterogeneity in funnel plots, i.e., plots of effect estimates against their estimated precision (reciprocal of the variance).[15] We examined funnel plot asymmetry visually and measured the degree of asymmetry by using Egger's unweighted regression asymmetry test.[16] If a study has appeared in more than one publication, data from the last publication were used for statistical analysis. We estimated the summary odds ratios and corresponding 95% confidence intervals (CIs) with random effects meta-regression analysis by using the Stata statistical software.[17] The between-study variance was estimated iteratively, by using the empiric Bayes method.[18] We analyzed the results for men and women both separately and combined, depending on available data in the original studies. To explore reasons for the observed heterogeneity, we performed sensitivity analyses on study characteristics and tested their influence on the association between current cigarette smoking and urinary tract cancer. We estimated the population attributable risk of urinary tract cancer for men and women based on the proportion of cigarette smokers in the European Union and the results of the current meta-analysis.

RESULTS

Study Characteristics

We identified 59 articles reporting follow-up or case–control studies on cigarette smoking and incident urinary tract cancer published between 1968 and 1998[19–77] (Table 1). Generally, the association between cigarette smoking and urinary tract cancer was not the main research hypothesis. Eighteen articles were excluded from the analyses because the same study appeared in publications that were more recent. The remaining 41 articles described 8 follow-up studies[40,44,52,60,67,69,70,72] and 35 case–control studies.[19–23,25,29,32,35,36,41,43,46,49,50,53–55,57–59,61,62,64–66,68,71,73–77] One case–control study that provided separate associations for parts of the study performed in the United States, United Kingdom, and Japan was considered as three separate studies.[29] The case–control studies were population-based (n = 12),[23,29,43,58,6165,66,71,75,77] hospital-based (n = 20)[19–22,25,32,35,36,38,49,50,54,55,57,59,64,68,73,74,76] or neighborhood-based (n = 1).[46] Two case–control studies used both population- and hospital-based controls.[53,62] The controls in most hospital-based case–control studies did not have any smoking-related disease. The case–control studies also varied with regard to their criteria of case selection. Thirteen case–control studies identified cancer cases in defined populations.[23,25,36,46,55,58,62,64–66,71,75,77] Twenty case–control studies selected cases from hospitals,[19,20–22,29,32,35,38,43,49,50,53,54,57,59,61,68,73,74,76] and two case–control studies used both populations and hospitals.[19,43] Information on cigarette smoking was obtained by interview (n = 29),[19–23,29,32,38,43,46,49,50,53–55,57–61,64–66,68,73–75] self-administered questionnaire (n = 12),[25,35,36,40,44,52,62,69,70,72,76,77] or both techniques (n = 1).[71] One follow-up study used medical files to obtain data on cigarette smoking.[67] Some studies included all neoplasms of the urinary tract as cases, of which greater than 90% were found to involve bladder cancer (n = 11).[29,35,40,57,60–62,72,76] Other studies defined case status by incident bladder cancer (n = 29),[19–21,23,25,32,36,38,43,44,49,50,52–55,59,64–71,73–75,77] carcinomas of the renal pelvis (n = 1),[22] or carcinomas of renal pelvis and ureter combined (n = 2).[46,58] Most studies used histologically confirmed cases with transitional cell carcinomas (Table 1).

Risk Estimation

We could not identify heterogeneity in funnel plots, neither visually nor in terms of statistical significance (P values ≥ 0.40 for current smoking) (Fig. 1). Tables 2 and 3 summarize the unadjusted and adjusted results of observational studies reporting the associations for different cigarette smoking characteristics, respectively.

Current cigarette smokers have approximately three times the risk of urinary tract cancer of nonsmokers. The adjusted summary odds ratios for current cigarette smokers compared with nonsmokers were 3.18 (CI, 2.35–4.29) for studies with men, 2.90 (CI, 2.01–4.19) for studies with women, and 3.33 (CI, 2.63–4.21) for studies with men and women combined (Table 3). Smoking cessation might be beneficial, although former smokers still have an increased risk of

TABLE 1
Study Characteristics of Published Epidemiologic Studies Concerning Cigarette Smoking and Cancer of the Urinary Tract, Ordered by Year of Publication

					Study design			
						Case–control study		
Ref.	First author	Year	Country	Anatomic site	Cohort study	Case source	Control source	Cigarette smoking assessment
19	Dunham	1968	U.S.	Bladder	—	Both	Hospital	Interview
20	Anthony	1970	U.K.	Bladder	—	Hospital	Hospital	Interview
21	Tyrrell	1971	Ireland	Bladder	—	Hospital	Hospital	Interview
22	Armstrong	1976	U.K.	Renal pelvis	—	Hospital	Hospital	Interview
23	Miller	1977	Canada	Bladder	—	Population	Population[a]	Interview
24[b]	Wynder	1977	U.S.	Bladder	—	Hospital	Hospital	Interview
25	Tola	1980	Finland	Bladder	—	Population	Hospital	Questionnaire[c]
26[b]	Vineis	1981	Italy	Bladder	—	Hospital	Hospital	Interview
27[b]	Vineis	1983	Italy	Urinary tract[d]	—	Hospital	Hospital	Interview
28[b]	Vineis	1984	Italy	Bladder	—	Hospital	Hospital	Interview
29	Morrison	1984	U.S./U.K./Japan	Urinary tract[d]	—	Hospital	Population	Interview
30[b]	Hartge	1985	U.S.	Bladder	—	Population	Population	Interview
31[b]	Marret	1985	U.S.	Bladder	—	Population	Population	Interview
32	Rebekalos	1985	Greece	Bladder	—	Hospital	Hospital	Interview
33[b]	Vineis	1985	Italy	Bladder	—	Hospital	Hospital	Interview
34[b]	Wynder	1985	U.S.	Bladder	—	Hospital	Hospital	Interview
35	Bravo	1986	Spain	Urinary tract[d]	—	Hospital	Hospital	Questionnaire[c]
36	Brownson	1987	U.S.	Bladder	—	Population	Hospital	Questionnaire[c]
37[b]	Hartge	1987	U.S.	Bladder	—	Population	Population	Interview
38[b]	Vineis	1988	Italy	Bladder	—	Hospital	Hospital	Interview
39[b]	Slatterly	1988	U.S.	Bladder	—	Population	Population	Interview
40	Steineck	1988	Sweden	Urinary tract[d]	Yes	—	—	Questionnaire[c]
41[b]	Augustine	1988	U.S.	Bladder	—	Hospital	Hospital	Interview
42[b]	La Vecchia	1989	Italy	Bladder	—	Hospital	Hospital	Interview
43	Burch	1989	Canada	Bladder	—	Both	Population	Interview
44	Helzlsouer	1989	U.S.	Bladder	Yes	—	—	Questionnaire[c]
45[b]	Clavel	1989	France	Bladder	—	Hospital	Hospital	Interview
46	Ross	1989	U.S.	Renal pelvis[e]	—	Population	Neighborhood	Interview
47[b]	D'Avanzo	1990	Italy	Bladder	—	Hospital	Hospital	Interview
48[b]	Hartge	1990	U.S.	Bladder	—	Population	Population	Interview
49	Iyer	1990	U.S.	Bladder	—	Hospital	Hospital	Interview
50[b]	Harris	1990	U.S.	Bladder	—	Hospital	Hospital	Interview
51[b]	La Vecchia	1991	Italy	Bladder	—	Hospital	Hospital	Interview
52	Mills	1991	U.S.	Bladder	Yes	—	—	Questionnaire[c]
53	Lopez-Abente	1991	Spain	Bladder	—	Hospital	Both	Interview
54	De Stefani	1991	Uruguay	Bladder	—	Hospital	Hospital	Interview
55	Burns	1991	U.S.	Bladder	—	Population	Hospital	Interview
56[b]	D'Avanzo	1992	Italy	Bladder	—	Hospital	Hospital	Interview
57	Kunze	1992	Germany	Urinary tract[d]	—	Hospital	Hospital	Interview
58	McLaughlin	1992	U.S.	Renal pelvis[e]	—	Population	Population	Interview
59[b]	Cordier	1993	France	Bladder	—	Hospital	Hospital	Interview
60	Chyou	1993	U.S.	Urinary tract[d]	Yes	—	—	Interview
61	Hayes	1993	U.S.	Urinary tract[d]	—	Hospital	Population	Interview
62	Sorahan	1994	U.K.	Urinary tract[d]	—	Population	Both[f]	Questionnaire[c]
63[b]	Barbone	1994	Italy	Bladder	—	Hospital	Hospital	Interview
64	Vizcaino	1994	Zimbabwe	Bladder	—	Population	Hospital	Interview
65	Momas	1994	France	Bladder	—	Population	Population	Interview
66	Sturgeon	1994	U.S.	Bladder	—	Population	Population	Interview
67	Tremblay	1995	Canada	Bladder	Yes	—	—	Medical files
68	D'Avanzo	1995	Italy	Bladder	—	Hospital	Hospital	Interview
69	McCarthy	1995	U.S.	Bladder	Yes	—	—	Questionnaire[c]
70	Murata	1996	Japan	Bladder	Yes	—	—	Questionnaire[c]
71	Bruemmer	1996	U.S.	Bladder	—	Population	Population	Both
72	Engeland	1996	Norwegen	Urinary tract[d]	Yes	—	—	Questionnaire[c]
73	Bedwani	1997	Egypt	Bladder	—	Hospital	Hospital	Interview
74	Donato	1997	Italy	Bladder	—	Hospital	Hospital	Interview
75	Teschke	1997	Canada	Bladder	—	Population	Population	Interview
76	Sorahan	1998	U.S.	Urinary tract[d]	—	Hospital	Hospital	Questionnaire[c]
77	Koivusalo	1998	Finland	Bladder	—	Population	Population	Questionnaire[c]

[a] And neighborhood.
[b] Study has appeared in more than one publication.
[c] Self-administered questionnaire.
[d] Includes bladder carcinoma and at least one other urinary tract cancer.
[e] And ureter.
[f] Only data from population controls were used.

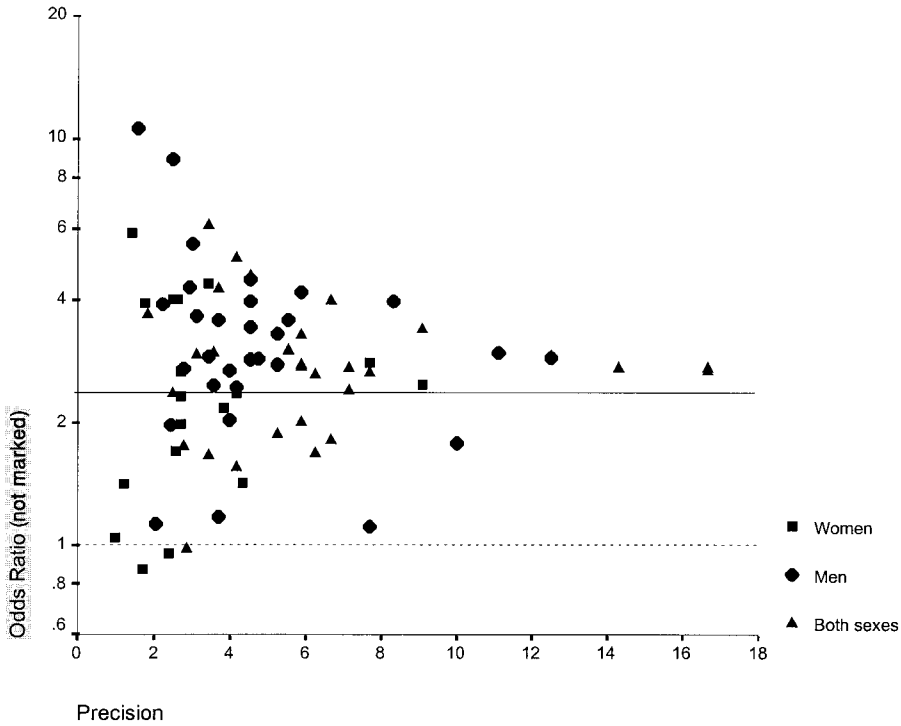

FIGURE 1. Funnel plot for current cigarette smokers compared with nonsmokers is shown. Dashed and solid reference lines indicate no effect and total summary odds ratio, respectively.

TABLE 2
Unadjusted Summary Odds Ratios for Different Cigarette Smoking Characteristics

	Male			Female			Male and Female		
Determinants	**n[a]**	**OR**	**CI**	**n[a]**	**OR**	**CI**	**n[a]**	**OR[b]**	**CI**
Smoking status									
Nonsmoker		1.00	Reference		1.00	Reference		1.00	Reference
Former smoker	23	2.00	1.57–2.55	12	1.66	1.13–2.44	22	1.71	1.51–1.94
Current smoker	24	2.81	2.31–3.43	15	2.33	1.82–2.99	23	2.57	2.20–3.00
Smoking amount									
Nonsmoker		1.00	Reference		1.00	Reference		1.00	Reference
1–20 cigarettes/day	11	2.34	1.77–3.09	7	1.79	1.39–2.30	14	2.17	1.75–2.70
> 20 cigarettes/day	11	2.91	2.09–4.06	5	2.57	2.24–2.94	14	2.79	2.00–3.90
Smoking duration (yrs)									
≤ 20		1.00	Reference		1.00	Reference		1.00	Reference
> 20	10	2.59	1.83–3.67	5	2.73	1.63–4.57	5	2.13	1.70–2.67
Smoking cessation (yrs)									
> 10		1.00	Reference		1.00	Reference		1.00	Reference
≤ 10	6	1.23	0.80–1.87	2	0.38	0.17–0.85	4	1.36	0.76–2.43
Age at first exposure (yrs)									
> 20		1.00	Reference		1.00	Reference		1.00	Reference
≤ 20	13	1.25	1.07–1.47	3	1.70	1.09–2.65	5	1.26	1.12–1.42

OR: odds ratio; CI: 95% confidence interval.
[a] No. of analyzed studies.
[b] Calculated from collapsed contingency tables.

urinary tract cancer compared with nonsmokers. The adjusted summary odds ratios for former smokers were 2.90 (CI, 1.41–5.98), 1.34 (CI, 1.03–1.74), and 1.98 (CI, 1.72–2.29) for studies with men only, women only, or men and women combined, respectively (Table 3).

The risk of urinary tract cancer is associated with the number of cigarettes smoked per day (Table 3). The adjusted summary odds ratios for smoking up to 20 cigarettes per day ranged from 1.66 (CI, 0.93–2.97) for studies with women to 2.66 (CI, 2.06–3.42) for

TABLE 3
Adjusted Summary Odds Ratios for Different Cigarette Smoking Characteristics

	Male			Female			Male and Female		
Determinants	n[a]	OR[b]	CI	n[a]	OR[b]	CI	n[a]	OR[c]	CI
Smoking status									
Nonsmoker		1.00	Reference		1.00	Reference		1.00	Reference
Former smoker	14	2.90	1.41–5.98	6	1.34	1.03–1.74	13	1.98	1.72–2.29
Current smoker	13	3.18	2.35–4.29	7	2.90	2.01–4.19	13	3.33	2.63–4.21
Smoking amount									
Nonsmoker		1.00	Reference		1.00	Reference		1.00	Reference
< 20 cigarettes/day	9	2.66	2.06–3.42	4	1.66	0.93–2.97	6	2.04	1.82–2.30
≤ 20 cigarettes/day	9	3.51	2.73–4.52	4	2.48	1.34–4.61	6	3.15	2.62–3.79

OR: odds ratio; CI: 95% confidence interval.
[a] No. of analyzed studies.
[b] Adjusted for age and gender.
[c] Adjusted for age.

studies with men. Men or women who smoked more than 20 cigarettes per day appeared to have higher risks. The adjusted summary odds ratios were: 3.51 (CI, 2.73–4.52), 2.48 (CI, 1.34–4.61), and 3.15 (CI, 2.62–3.79) for studies with men only, women only, or men and women combined, respectively (Table 3).

For both smoking status and smoking amount, the unadjusted estimation for the summary odds ratios were usually lower than the age- and gender-adjusted estimates, although the unadjusted estimates were based on a larger set of studies (Table 2). For smoking duration, smoking cessation, and age at first exposure of smoking, only unadjusted summary odds ratios could be calculated.

The risk of urinary tract cancer increased with increasing duration of cigarette smoking (Table 2). Subjects who smoked for greater than 20 years appeared to develop urinary tract cancer at 2–3 times the rate in subjects who smoked cigarettes for less than 20 years. The corresponding summary odds ratios were 2.59 (CI, 1.83–3.67) for studies with men, 2.73 (CI, 1.63–4.57) for studies with women, and 2.13 (CI, 1.70–2.67) for studies in which the data for men and women were collapsed (Table 2).

The time since smoking cessation among former smokers also appeared to be an important smoking characteristic (Table 2). Men who stopped smoking for less than 10 years had higher risks of urinary tract cancer compared with men who stopped smoking for longer than 10 years (summary odds ratio, 1.23; CI, 0.80–1.87). However, the reduction in risk for women appeared to be greatest in the first decade after quitting, although this is only based on two case–control studies (summary odds ratio, 0.38; CI, 0.17–0.85).[43,57] The summary odds ratio for studies with collapsed data on men and women was 1.36 (CI, 0.76–2.43) (Table 2).

Furthermore, persons who started smoking at younger ages (younger than 20 years) tended to have higher risks of urinary tract cancer compared with persons who start smoking at older ages (Table 2). The corresponding summary odds ratios were 1.25 (CI, 1.07–1.47) for studies with men, 1.70 (CI, 1.09–2.65) for studies with women, and 1.26 (CI, 1.12–1.42) for studies with men and women combined (Table 2).

Sensitivity Analysis

We further examined the crude association of current smoking by geographic area, year of publication, study design, measuring instrument, sources of cases and controls, and anatomic site of the tumor to explore their influence on the outcome estimates in studies that provided information for men and women combined (Fig. 2). No tests for interaction were statistically significant. Most subset specific summary odds ratios did not differ substantially, although it appeared that the odds ratios from studies published before 1980 were lower than from more recent studies. Furthermore, the summary associations for case–control studies were higher than for follow-up studies. Selection on anatomic site of the tumor did not alter the summary odds ratios (Fig. 2).

Population Attributable Risk

In the European Union, 28% of women and 43% of men smoke cigarettes.[78] Based on these figures and the age-adjusted results of the current meta-analysis, our estimates show that cigarette smoking might account for 34.7% of all female urinary tract cancer,

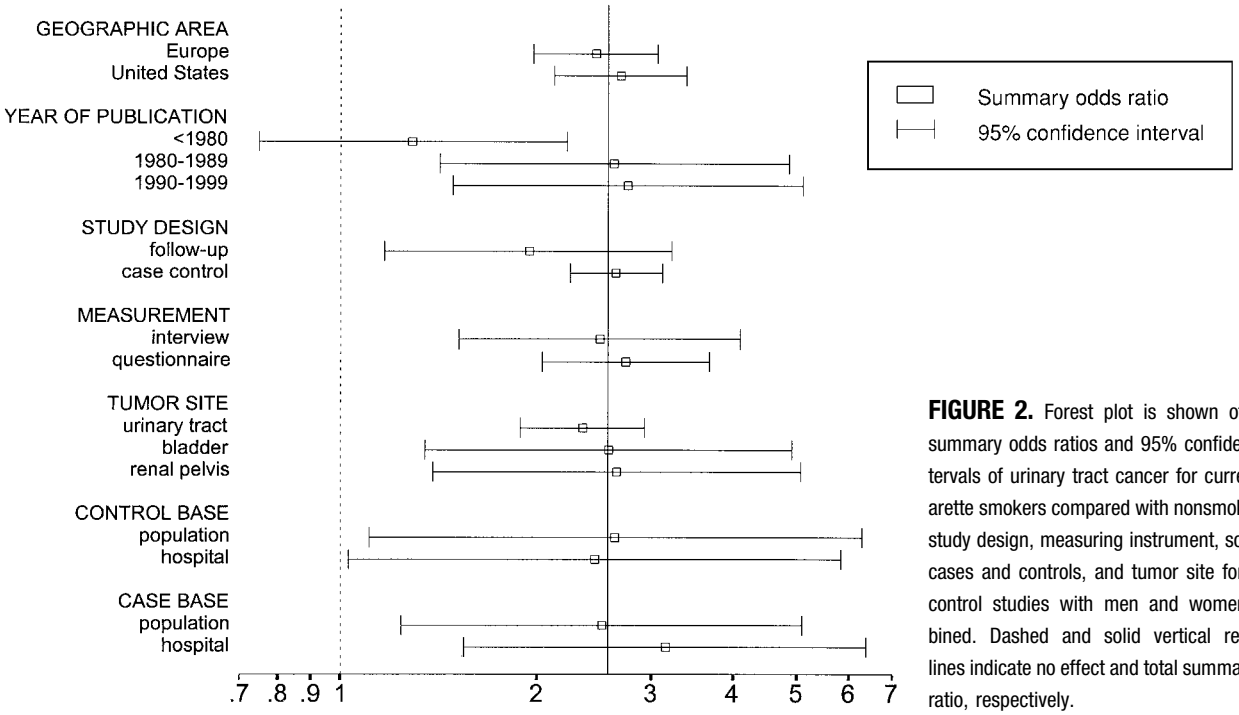

FIGURE 2. Forest plot is shown of crude summary odds ratios and 95% confidence intervals of urinary tract cancer for current cigarette smokers compared with nonsmokers, by study design, measuring instrument, source of cases and controls, and tumor site for case–control studies with men and women combined. Dashed and solid vertical reference lines indicate no effect and total summary odds ratio, respectively.

whereas in men 50.0% of incidences of the disease may be associated with cigarette smoking.

DISCUSSION

The possible association between cigarette smoking and cancer of the urinary tract has been extensively investigated in 43 epidemiologic studies. These primary studies can be considered as the best available evidence. The summarized findings suggest a substantial increase of risk of urinary tract cancer for cigarette smokers. Smoking amount and smoking duration were positively associated with urinary tract cancer risk. For age at first exposure and smoking cessation, a negative association was found.

Unfortunately, the included studies did not provide sufficient information to estimate adjusted summary odds ratios for all smoking characteristics. For smoking duration, smoking cessation, and age at first exposure of smoking only unadjusted summary odds ratios could be calculated. The summary odds ratios for smoking status and smoking amount increased after adjustment for age and gender. Therefore, we expect the crude estimates for smoking duration, smoking cessation, and age at first exposure to be underestimated.

We did not attempt to uncover unpublished observations and excluded studies that did not meet the predetermined criteria. Publication bias might arise by excluding these studies. However, we could not identify funnel plot heterogeneity in our meta-analysis, either visually or in terms of statistical significance.

Because of potential heterogeneity in populations, designs, and analyses of various studies, we assumed that the true effects being estimated would vary between the studies in addition to the usual sampling variation in the estimates (within studies). To account for both sources of variation, we used random effects meta-regression analysis to combine the results from the primary studies.[18] The random effect approach provides some allowance for heterogeneity in studies beyond sampling error.

The epidemiology of urinary tract cancer is rather complex. For example: substantial differences exist in urinary tract cancer rates between white and black people; urinary tract cancer is considerably more common in men than in women; and the incidence of this cancer varies between North America and Europe.[79] The race of the study population in almost all component studies was white. Therefore, the influence of race on the association between cigarette smoking and urinary tract cancer could not be investigated in the current meta-analysis. For both men and women, we found similarly increased urinary tract cancer risks for cigarette smoking. Furthermore, the summary odds ratios were similar for different geographic areas.

Results from sensitivity analyses suggested that the summary odds ratios were comparable for differ-

ent types of exposure measurement, for different tumor sites, and for different sources of the cases and controls in the case–control studies. The summary estimates were also similar between the different years of publication, although studies published before 1980 yielded to a lower summary odds ratio than studies published after 1980. This difference could not be explained by diversity in population or methodology between studies published before and after 1980 and is probably an artifact of chance. It appeared that the summary estimates of case–control studies were somewhat higher than for follow-up studies. This contrast, although not statistically significant, might be a consequence of differential recall bias in case–control studies because patients with bladder cancer are possibly more sensitized toward recalling smoking habits than noncases.

The precise mechanism by which cigarette smoking causes urinary tract cancer has yet to be determined. The finding that both age at first exposure and cessation of exposure have an influence in modifying the summary odds ratio of urinary tract cancer might suggest that two stages in the mechanism of urinary tract carcinogenicity are involved, one early and one late.[80] However, few studies simultaneously included different smoking characteristics in a regression model to estimate the independent contribution of these smoking characteristics. It seems most likely that the risk of urinary tract cancer is related to some of the large number of chemicals present in smoke. 2-Naphthylamine and 4-aminobiphenyl are the leading candidates as the specific etiologic agents.[3,8,9,81,82] Several nitrosamines have been shown to produce bladder cancer in animal models.[9] Tars might induce bladder papillomas and carcinomas in mice.[8] To our knowledge, no epidemiologic study on the association between tars and nicotine exposure and bladder cancer risk has been conducted, although one case–control study reported a diminution of risk from the smoking of light tobacco.[53] Molecular studies have suggested that exposure to certain carcinogens in cigarette smoke may contribute to DNA damage, i.e., chromosome 9 defects[83] and TP53 mutations.[84] These alterations are the most frequently known molecular abnormalities in the etiology of bladder cancer.[83] Furthermore, genetic polymorphisms, e.g., of the arylamine *N*-acetyltransferase or glutathione *S*-transferase Mu1 (GSTM1), may alter metabolism of tobacco carcinogens. Slow acetylation or lack of GSTM1 activity (which is present in 50% of whites) might result in a higher concentration of tobacco carcinogens in the bladder and consequently enhance the risk of bladder cancer among cigarette smokers.[85–7] Unfortunately, the data of the current meta-analysis could not be stratified upon these or other polymorphisms. Besides the effect that many compounds in cigarettes can cause genotoxic events in the urothelium, cigarette smoking have been found to increase proliferation, as evidenced by hyperplasia of the urinary tract epithelium.[9]

In accordance with earlier reviews, it can be concluded that cigarette smoking is an important cause of urinary tract cancer for both men and women. Current cigarette smokers have an approximately threefold higher risk of urinary tract cancer than nonsmokers. This risk increases with the number of cigarettes smoked per day and the number of years smoked. Both age at first exposure and cessation of cigarette smoking have an influence on modifying the risk of urinary tract cancer. Approximately half of male urinary tract cancer and one-third of female urinary tract cancer might be attributable to cigarette smoking.

REFERENCES

1. Morrison AS. Advances in the etiology of urothelial cancer. *Urol Clin North Am* 1984;11:557–66.
2. Matanoski GM, Elliott EA. Bladder cancer epidemiology. *Epidemiol Rev* 1981;3:203–29.
3. Dolin PJ. An epidemiological review of tobacco use and bladder cancer. *J Smoking Related Dis* 1991;2:129–43.
4. Silverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. *Hematol Oncol Clin North Am* 1992;6:1–30.
5. Shirai T. Etiology of bladder cancer. *Semin Urol* 1993;11: 113–26.
6. Shirai T, Fradet Y, Huland H, Bollack C, Droller M, Janknegt R, et al. The etiology of bladder cancer: are there any new clues or predictors of behavior? *Int J Urol* 1995;2(3 Suppl): 64–75.
7. Silverman DT, Morrison AS, Devesa SS. Bladder cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York and Oxford: Oxford University Press, 1996:1156–79.
8. Ross RK, Jones PA, Yu MC. Bladder cancer epidemiology and pathogenesis. *Semin Oncol* 1996;23:536–45.
9. Johansson SL, Cohen SM. Epidemiology and etiology of bladder cancer. *Semin Surg Oncol* 1997;13:291–8.
10. World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans: tobacco smoking. Lyon: IARC, 1986.
11. Van der Meijden APM. Bladder cancer. *Br Med J* 1998;317: 1366–9.
12. Zeegers MPA, Tan FES, Verhagen AP, Weijenberg MP, van den Brandt PA. Elevated risk of cancer of the urinary tract for alcohol drinkers: a meta-analysis. *Cancer Causes Control* 1999;10:445–51.
13. Woolf B. On estimation the relation between blood group and disease. *Ann Hum Genet* 1954;19:251–3.
14. Tan FES, Zeegers MPA. An alternative method of combining exposure specific odds ratios in epidemiologic studies. Research report. Maastricht: Maastricht University, Department Methodology and Statistics, 1999.
15. Light RJ, Pillemer DB. Quantitative procedures. In: Summing up: the science of reviewing research. Cambridge, MA: Harvard University Press, 1984.

16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997;315:629–34.
17. StataCorp Stata Statistical Software. Release 6.0. College Station, TX: Stata Corporation, 1999.
18. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Stat Med* 1995; 14:395–411.
19. Dunham LJ, Rabson AS, Steward HS, Frank A, Young JL. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. *J Natl Cancer Inst* 1968;41:683–709.
20. Anthony HM, Thomas GM. Bladder tumours and smoking. *Int J Cancer* 1970;5:266–72.
21. Tyrrell AB, MacAirt JG, McCaughey WT. Occupational and non-occupational factors associated with vesical neoplasm in Ireland. *J Ir Med Assoc* 1971;64:213–7.
22. Armstrong B, Garrod A, Doll R. A retrospective study of renal cancer with special reference to coffee and animal protein consumption. *Br J Cancer* 1976;33:127–36.
23. Miller AB, Howe GR. Artificial sweeteners and bladder cancer. *Lancet* 1977;10:1221–2.
24. Wynder EL, Goldsmith R. The epidemiology of bladder cancer: a second look. *Cancer* 1977;40:1246–68.
25. Tola S, Tenho M, Korkala ML, Jarvinen E. Cancer of the urinary bladder in Finland: association with occupation. *Int Arch Occup Environ Health* 1980;46:43–51.
26. Vineis P, Segnan N, Costa G, Terracini B. Evidence of a multiplicative effect between cigarette smoking and occupational exposures in the aetiology of bladder cancer. *Cancer Lett* 1981;14:285–90.
27. Vineis P, Frea B, Uberti E, Ghisetti V, Terracini B. Bladder cancer and cigarette smoking in males: a case-control study. *Tumori* 1983;69:17–22.
28. Vineis P, Esteve J, Terracini B. Bladder cancer and smoking in males: types of cigarettes, age at start, effect of stopping and interaction with occupation. *Int J Cancer* 1984;34:165–70.
29. Morrison AS, Buring JE, Verhoek WG, Aoki K, Leck I, Ohno Y, et al. An international study of smoking and bladder cancer. *J Urol* 1984;131:650–4.
30. Hartge P, Hoover R, Kantor A. Bladder cancer risk and pipes, cigars and smokeless tobacco. *Cancer* 1985;15:901–6.
31. Marrett LD, Meigs JW, Flannery JT. Bladder cancer in Connecticut: the role of cigarette smoking and other risk factors. *Conn Med* 1985;49:718–26.
32. Rebekalos A, Trichopoulos D, Tzonou A, Zavitsanos X, Velonakis E, Trichopoulos A. Tobacco smoking, coffee drinking, and occupation as risk factors for bladder cancer in Greece. *J Natl Cancer Inst* 1985;75:455–61.
33. Vineis P, Ciccone G, Ghisetti V, Terracini B. Cigarette smoking and bladder cancer in females. *Cancer Lett* 1985;26:61–6.
34. Wynder EL, Dieck GS, Hall NE, Lahti H. A case-control study of diesel exhaust exposure and bladder cancer. *Environ Res* 1985;37:475–89.
35. Bravo P, del Rey Calero J, Sanchez J, Conde M. El tabaco como factor de riesgo del cancer de vejiga. *Arch Esp Urol* 1986;39:237–40.
36. Brownson RC, Chang JC, Davis JR. Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *Am J Public Health* 1987;77:1298–300.
37. Hartge P, Silverman D, Hoover R, Schairer C, Altman R, Austin D, et al. Changing cigarette habits and bladder cancer risk: a case-control study. *J Natl Cancer Inst* 1987;78: 1119–25.
38. Vineis P, Esteve J, Hartge P, Hoover R, Silverman DT, Terracini B. Effects of timing and type of tobacco in cigarette-induced bladder cancer. *Cancer Res* 1988;48:3849–52.
39. Slattery ML, Schumacher MC, West DW, Robison LM. Smoking and bladder cancer. The modifying effect of cigarettes on other factors. *Cancer* 1988;61:402–8.
40. Steineck G, Norell SE, Feychting M. Diet, tobacco and urothelial cancer: a 14-year follow-up of 16,477 subjects. *Acta Oncol* 1988;27:323–7.
41. Augustine A, Hebert JR, Kabat GC, Wynder EL. Bladder cancer in relation to cigarette smoking. *Cancer Res* 1988;48: 4405–8.
42. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Liberati C, Franceschi S. Dietary factors in the risk of bladder cancer. *Nutr Cancer* 1989;12:93–101.
43. Burch JD, Rohan TE, Howe GR, Risch HA, Hill GB, Steele R, et al. Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer* 1989;44:622–8.
44. Helzlsouer KJ, Comstock GW, Morris JS. Selenium, lycopene, alpha-tocopherol, beta-carotene, retinol, and subsequent bladder cancer. *Cancer Res* 1989;49:6144–8.
45. Clavel J, Cordier S, Boccon Gibod L, Hemon D. Tobacco and bladder cancer in males: increased risk for inhalers and smokers of black tobacco. *Int J Cancer* 1989;44:605–10.
46. Ross RK, Paganini Hill A, Landolph J, Gerkins V, Henderson BE. Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter. *Cancer Res* 1989;49: 1045–8.
47. D'Avanzo B, Negri E, La Vecchia C, Gramenzi A, Bianchi C, Franceschi S, et al. Cigarette smoking and bladder cancer. *Eur J Cancer* 1990;26:714–8.
48. Hartge P, Harvey EB, Marston Linehan W, Silverman DT, Sullivan JW, Hoover RN, et al. Unexplained excess risk of bladder cancer in men. *J Natl Cancer Inst* 1990;82:1636–40.
49. Iyer V, Harris RE, Wynder EL. Diesel exhaust exposure and bladder cancer risk. *Eur J Epidemiol* 1990;6:49–54.
50. Harris RE, Chen Backlund JY, Wynder EL. Cancer of the urinary bladder in blacks and whites: a case-control study. *Cancer* 1990;66:2673–80.
51. La Vecchia C, Negri E, D'Avanzo B, Savoldelli R, Franceschi S. Genital and urinary tract diseases and bladder cancer. *Cancer Res* 1991;51:629–31.
52. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. *Am J Epidemiol* 1991;133:230–9.
53. Lopez-Abente G, Gonzalez CA, Errezola M, Escolar A, Izarzugaza I, Nebot M, et al. Tobacco smoke inhalation pattern, tobacco type, and bladder cancer in Spain. *Am J Epidemiol* 1991;134:830–9.
54. De Stefani E, Correa P, Fierro L, Fontham E, Chen V, Zavala D. Black tobacco, mate, and bladder cancer: a case-control study from Uruguay. *Cancer* 1991;67:536–40.
55. Burns PB, Swanson GM. Risk of urinary bladder cancer among blacks and whites: the role of cigarette use and occupation. *Cancer Causes Control* 1991;2:371–9.
56. D'Avanzo B, La Vecchia C, Franceschi S, Negri E, Talamini R, Buttino I. Coffee consumption and bladder cancer risk. *Eur J Cancer* 1992;28a:1480–4.
57. Kunze E, Chang Claude J, Frentzel Beyme R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer* 1992;69:1776–90.

58. McLaughlin JK, Silverman DT, Hsing AW, Ross RK, Schoenberg JB, Yu MC, et al. Cigarette smoking and cancers of the renal pelvis and ureter. *Cancer Res* 1992;52:254–7.
59. Cordier S, Clavel J, Limasset JC, Boccon Gibod L, Le Moual N, Mandereau L, et al. Occupational risks of bladder cancer in France: a multicentre case-control study. *Int J Epidemiol* 1993;22:403–11.
60. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol* 1993;3:211–6.
61. Hayes RB, Friedell GH, Zahm SH, Cole P. Are the known bladder cancer risk-factors associated with more advanced bladder cancer? *Cancer Causes Control* 1993;4:157–62.
62. Sorahan T, Lancashire RJ, Sole G. Urothelial cancer and cigarette smoking: findings from a regional case-controlled study. *Br J Urol* 1994;74:753–6.
63. Barbone F, Franceschi S, Talamini R, Bidoli E, La Vecchia C. Occupation and bladder cancer in Pordenone (north-east Italy): a case-control study. *Int J Epidemiol* 1994;23:58–65.
64. Vizcaino AP, Parkin DM, Boffetta P, Skinner MEG. Bladder cancer: epidemiology and risk factors in Bulawayo, Zimbabwe. *Cancer Causes Control* 1994;5:517–22.
65. Momas I, Daures JP, Festy B, Bontoux J, Gremy F. Bladder cancer and black tobacco cigarette smoking. Some results from a French case-control study. *Eur J Epidemiol* 1994;10:599–604.
66. Sturgeon SR, Hartge P, Silverman DT, Kantor AF, Linehan WM, Lynch C, et al. Associations between bladder cancer risk factors and tumor stage and grade at diagnosis. *Epidemiology* 1994;5:218–25.
67. Tremblay C, Armstrong B, Theriault G, Brodeur J. Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. *Am J Ind Med* 1995;27:335–48.
68. D'Avanzo B, La Vecchia C, Negri E, Decarli A, Benichou J. Attributable risks for bladder cancer in northern Italy. *Ann Epidemiol* 1995;5:427–31.
69. McCarthy PV, Bhatia AJ, Saw SM, Mosley JD, Vega-Quinones A. Cigarette smoking and bladder cancer: in Washington County, Maryland: ammunition for health educators. *Md Med J* 1995;44:1039–42.
70. Murata M, Takayama K, Choi BC, Pak AW. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. *Cancer Detect Prev* 1996;20:557–65.
71. Bruemmer B, White E, Vaughan TL, Cheney CL. Nutrient intake in relation to bladder cancer among middle-aged men and women. *Am J Epidemiol* 1996;144:485–95.
72. Engeland A, Andersen A, Haldorsen T, Tretli S. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. *Cancer Causes Control* 1996;7:497–506.
73. Bedwani R, el Khwsky F, Renganathan E, Braga C, Abu Seif HH, Abul Azm T, et al. Epidemiology of bladder cancer in Alexandria, Egypt: tobacco smoking. *Int J Cancer* 1997;73:64–7.
74. Donato F, Boffetta P, Fazioli R, Aulenti V, Gelatti U, Porru S. Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia northern Italy. *Eur J Epidemiol* 1997;13:795–800.
75. Teschke K, Morgan MS, Checkoway H, Franklin G, Spinelli JJ, Van belle G, et al. Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens. *Occup Environ Med* 1997;54:443–51.
76. Sorahan T, Hamilton L, Wallace DM, Bathers S, Gardiner K, Harrington JM. Occupational urothelial tumours: a regional case-control study. *Br J Urol* 1998;82:25–32.
77. Koivusalo M, Hakulinen T, Vartiainen T, Pukkala E, Jaakkola JJK, Tuomisto J. Drinking water mutagenicity and urinary tract cancers: a population based cancer control study in Finland. *Am J Epidemiol* 1998;148:704–12.
78. Statistical Office of the European Communities. Social portrait of Europe. Luxembourg: Office for Official Publications of the European Communities, 1996.
79. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999;80:827–41.
80. Vineis P. Tobacco and cancer: an update. *Crit Rev Oncol Hematol* 1995;18:103–10.
81. Morrison AS, Cole P. Epidemiology of bladder cancer. *Urol Clin North Am* 1976;3:13–29.
82. Vineis P. Epidemiological models of carcinogenesis: the example of bladder cancer. *Cancer Epidemiol Biomarkers Prev* 1992;1:149–53.
83. Zhang ZF, Shu XM, Cordon Cardo C, Orlow I, Lu ML, Millon TV, et al. Cigarette smoking and chromosome 9 alterations in bladder cancer. *Cancer Epidemiol Biomarkers Prev* 1997;6:321–6.
84. Spruck CH III, Rideout WM III, Olumi AF, Ohneseit PF, Yang AS, Tsai YC, et al. Distinct pattern of p53 mutations in bladder cancer: relationship to tobacco usage [published erratum appears in *Cancer Res* 1993;53(10 Suppl):2427]. *Cancer Res* 1993;53:1162–6.
85. Brockmoller J, Cascorbi I, Kerb R, Roots I. Combined analysis of inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1, microsomal epoxide hydrolase, and cytochrome P450 enzymes as modulators of bladder cancer risk. *Cancer Res* 1996;56:3915–25.
86. Brockmoller J, Kerb R, Drakoulis N, Staffeldt B, Roots I. Glutathione S-transferase M1 and its variants A and B as host factors of bladder cancer susceptibility: a case-control study. *Cancer Res* 1994;54:4103–11.
87. Bartsch H, Malaveille C, Friesen M, Kadlubar FF, Vineis P. Black (air-cured) and blond (flue-cured) tobacco cancer risk. IV: molecular dosimetry studies implicate aromatic amines as bladder carcinogens. *Eur J Cancer* 1993;29a:1199–207.