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INVITED ARTICLE

Tobacco smoking and risk of bladder cancer

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Abstract
Tobacco smoking is the main known cause of urinary bladder cancer in humans. In most populations, over half of cases in men and a sizeable proportion in women are attributable to this habit. Epidemiological studies conducted in different populations have shown a linear relationship between intensity and duration of smoking and risk. Quitting smoking reduces the risk of bladder cancer. Smoking black (air-cured) cigarettes results in a higher risk than smoking blond (flue-cured) tobacco cigarettes; results on inhalation patterns and use of filter are not consistent. Cigar and pipe smoking also increases the risk of bladder cancer; data on other tobacco products are limited. The evidence for non-transitional bladder carcinoma is limited, but consistent with an increased risk. The available evidence does not point towards a different carcinogenic effect of tobacco smoking in men and women or in whites and blacks. Data on involuntary smoke and use of smokeless tobacco products are limited, but do not suggest an increased risk of bladder cancer.

Key Words: *Involuntary smoke, smokeless tobacco, tobacco smoking, urinary bladder cancer*

Introduction

Tobacco smoking is a cause of urinary bladder cancer. An association has been observed in epidemiological studies conducted since the late 1950s [1], and its causal nature was established in the 1980s [2,3]. An increased risk of bladder cancer among smokers has been reported in studies conducted in Asia, North and South America, Africa, Europe and Oceania.

In a recent meta-analysis of studies published up to 2003, Gandini et al. estimated an overall relative risk of cancer of the lower urinary tract (predominantly bladder cancer) for current smokers of 2.77 [95% confidence interval (CI) 2.17, 3.54], based on 36 risk estimates from 21 studies [4]. The corresponding relative risk for former smoking, based on 15 studies, was 1.72 (95% CI 1.46, 2.04). The summary relative risk for current smoking was comparable in men and women, in cohort and case–control studies, and in whites and blacks (Table I).

Intensity of smoking, duration of smoking and age at start

Many epidemiological studies have addressed specific aspects of the carcinogenic effect of tobacco smoking on the urinary bladder. The results of cohort studies on intensity of smoking are summarized in Table II. More than 30 case–control studies have provided similar results: they are summarized in the latest International Agency for Research on Cancer (IARC) Monograph [22]. In general, intensity of smoking displays a monotonic relationship with risk, with no evidence of a threshold. Data on heavy smokers are relatively sparse, and it is unclear whether the risk keeps increasing or there is a plateau at high doses (e.g. because of saturation of activating pathways).

Results on duration of smoking are mainly available from case–control studies (Table III). An increase in risk is present even for short duration of smoking, and in most studies that reported results for very long-term smoking, there was no clear

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Table I. Meta-analysis of current tobacco smoking and risk of bladder cancer [4].

Category	*N* risk estimates	RR	95% CI	*p*-Value of test of interaction
Gender				
Men	9	2.80	2.01, 3.92	0.87
Women	14	2.73	1.82, 4.10	
Study design				
Cohort	5	2.05	1.19, 3.55	0.21
Case–control	15	3.00	2.26, 3.97	
Ethnic group				
White	7	3.39	1.23, 9.33	0.54
Black	2	2.34	0.35, 15.9	

RR = relative risk; CI = confidence interval.

Table II. Results of cohort studies on intensity of tobacco smoking and risk of urinary bladder cancer.

Reference	Country, gender	Intensity of smoking (cigarettes/day)	RR	95% CI
[1,5]	USA, men	1–9	2.0	NA
		10–20	2.0	NA
		21+	3.4	NA
[6]	USA, men	1–9	1.0	NA
		10–20	2.3	NA
		21–39	3.1	NA
		40+	3.0	NA
[7]	Canada, men	1–9	1.3	NA
		10–20	1.4	NA
		21+	1.4	NA
[8]	USA, men	1–9	1.5	NA
		10–20	2.8	NA
		21+	5.4	NA
[9]	Sweden, men	1–7	1.5	NA
		8–15	1.6	NA
		16+	2.7	NA
[21]	women	1–7	1.2	NA
		8–15	2.1	NA
		16+	0.8	NA
[10]	UK, men	1–14	[2.2]	NA
		15–24	[2.2]	NA
		25+	[1.4]	NA
[11]	Sweden, men	1–9	4.5	2.1, 9.9
		10+	4.7	2.0, 10.8
[12]	Japan, men	1–4	1.8	0.4, 5.0
		5–14	1.4	0.9, 2.3
		15–24	2.0	1.3, 3.3
		25–34	1.7	0.6, 4.1
		35+	2.1	0.5, 6.1
	women	1–4	0.9	0.1, 4.0
		5–14	2.2	1.1, 4.1
		15+	1.2	0.1, 5.7
[13]	USA, men	1–15	[1.1]	NA
		16–25	[1.9]	NA
		26–35	[2.7]	NA
		36–45	[2.4]	NA
		46+	[2.3]	NA
[14]	USA, men and women	1–14	1.6	0.6, 4.1
		15–24	4.3	1.9, 9.7
		25+	3.3	1.3, 8.6
[15]	UK, men	1–14	[2.2]	NA
		15–24	[2.2]	NA
		25+	[2.8]	NA
[16]	USA, men	1–9	1.1	0.8, 1.5
		10–20	2.3	1.9, 2.7

Table II (*Continued*)

Reference	Country, gender	Intensity of smoking (cigarettes/day)	RR	95% CI
		21–39	2.7	2.2, 3.3
		40+	2.2	1.5, 3.3
[17]	Norway, men	1–4	2.5	1.5, 4.0
		5–9	2.7	1.6, 4.5
		10–14	3.4	2.1, 5.4
		15+	5.1	3.1, 8.4
	women	1–4	1.5	0.7, 3.2
		5–9	2.2	1.0, 4.7
		10–14	5.4	2.8, 11
		15+	7.9	2.2, 19
		1–10	2.6	NA
[18]	Japan, men	11–20	2.3	NA
		21+	1.3	NA
[19]	China, men	1–19	2.1	NA
		20+	1.7	NA
[20]	Sweden, women	1–7	1.9	1.0, 3.6
		8–15	2.9	1.4, 5.8
		16+	3.4	1.2, 9.7
[21]	Iceland, men	1–14	1.5	0.7, 3.0
		15–24	2.6	1.4, 4.7
		25+	4.6	2.4, 6.9

Figures in square brackets = results obtained from raw data reported in the original publication.
RR = relative risk; CI = confidence interval; NA = not available.

Table III. Results of case–control studies on duration of tobacco smoking and risk of urinary bladder cancer.

Reference	Country, gender	Duration of smoking (years)	RR	95% CI
[23]	Canada, men	1–10	1.6	0.9, 2.7
		11–20	1.5	0.9, 2.5
		21–30	1.8	1.2, 2.9
		31+	2.3	1.6, 3.4
	women	1–10	0.8	0.3, 2.0
		11–20	1.1	0.5, 2.8
		21–30	3.4	1.4, 7.9
		31+	2.2	1.3, 3.7
[24]	Germany, women	1–20	5.4	1.4, 21
		21–40	1.1	0.4, 3.1
		41+	10	1.9, 56
[25]	France, men	1–9	1.8	0.9, 3.6
		10–19	1.9	1.0, 3.5
		20–29	2.8	1.7, 4.8
		30–39	5.2	3.2, 8.4
		40–49	5.2	3.2, 8.5
		50+	4.8	2.6, 8.9
[26]	Italy, men	1–29	1.7	0.9, 3.1
		30+	3.1	1.9, 4.9
	women	1–29	1.5	0.3, 6.8
		30+	4.6	1.6, 14
[27]	USA, men	1–10	[1.2]	[0.8, 1.8]
		11–20	[1.4]	[1.0, 1.8]
		21–30	[2.0]	[1.6, 2.5]
		31–40	[2.3]	[1.9, 2.9]
		41+	[3.0]	[2.5, 3.6]
	women	1–10	[0.8]	[0.4, 1.5]
		11–20	[1.1]	[0.7, 2.0]
		21–30	[1.9]	[1.2, 3.0]
		31–40	[2.4]	[1.8, 3.3]
		41+	[3.7]	[2.9, 4.7]
[28]	Uruguay, men	1–29	2.7	0.6, 12
		30–39	9.5	2.3, 39

Table III (*Continued*)

Reference	Country, gender	Duration of smoking (years)	RR	95% CI
		40–49	9.4	2.6, 34
		50+	8.7	8.7, 31
[29]	Spain, men	1–19	1.8	0.9, 3.5
		20–39	3.9	2.4, 6.5
		40–59	4.7	2.9, 7.5
		60+	4.4	2.0, 9.8
[30]	Germany, men	1–19	1.1	0.7, 1.7
		20–39	2.6	1.6, 3.3
		40+	3.7	2.6, 5.3
	women	1–19	3.8	1.4, 10
		20–39	1.3	0.5, 3.4
		40+	5.6	2.0, 15
[31]	USA, men	1–25	2.4	1.1, 5.5
		26–37	3.1	1.5, 6.7
		38–45	4.7	2.1, 11
		46+	5.9	2.6, 14
	women	1–25	0.9	0.3, 2.2
		26–27	1.4	0.6, 3.4
		38–45	2.2	1.0, 4.9
		46+	7.9	2.8, 23
[32]	France, men	1–39	2.9	1.2, 6.8
		40–55	5.3	2.8, 9.9
		56+	7.1	3.3, 15
[33]	UK, men	1–9	0.9	0.6, 1.5
		10–19	1.4	1.0, 1.9
		20–29	1.8	1.4, 2.5
		30–39	2.5	1.8, 3.3
		40+	2.9	2.2, 3.8
[34]	Germany, men	1–19	1.8	0.9, 3.3
		20–39	2.8	1.5, 5.2
		40+	5.0	2.6, 9.6
	women	1–19	2.1	1.1, 3.9
		20–39	3.0	1.7, 5.4
		40+	3.4	1.6, 7.2
[35]	USA, men	1–9	1.2	0.8, 1.7
		10–19	1.4	1.1, 1.9
		20–29	2.4	1.8, 3.2
		30–39	3.3	2.5, 4.3
		40+	4.2	3.1, 5.6
	women	1–9	0.8	0.4, 1.7
		10–19	1.5	0.9, 2.8
		20–29	2.3	1.4, 3.9
		30–39	5.4	3.2, 9.2
		40+	6.0	3.1, 12

Figures in square brackets = results obtained from raw data reported in the original publication.
RR = relative risk; CI = confidence interval.

evidence of a plateau in the excess risk. Since duration and intensity of smoking my be correlated, it is of interest to explore the effect of one variable while stratifying for the other one. This type of analysis requires large number of individuals, which were available in only a few studies. Figure 1 summarizes the results of such a stratified analysis, based on a pooled set of 2600 male cases and 5524 controls from 11 European studies [36]: despite some imprecision in the categories with few subjects (e.g. short-term heavy smokers), this analysis provides strong evidence for an independent effect of the two aspects of smoking.

A clear effect of age at start smoking was observed in studies conducted in various countries (Table IV). These risk estimates, however, were not adjusted for duration or intensity of smoking, and it is not possible to conclude to what extent they reflect residual confounding.

Effect of quitting

As mentioned above, former smokers have a lower risk than current smokers. In addition, several studies reported results according to time since quitting; these are summarized in Table V. Although an effect

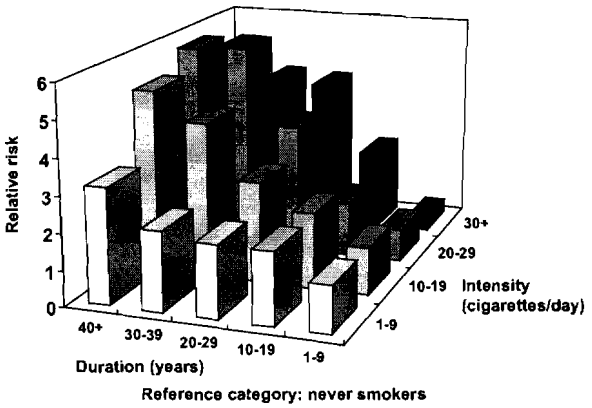


Figure 1. Relative risk of urinary bladder cancer for intensity and duration of tobacco smoking. Pooled analysis of 11 European case-control studies [36].

of quitting is reported in most studies, there is little evidence that the excess risk disappears even after a long time since quitting. In the pooled analysis of case-control studies form Europe, the effect of quitting was not confounded by intensity of smoking (i.e. the reduced risk among quitters due to light smokers being more likely to quit than heavy smokers) [36,41].

Effect of inhalation, use of filter and type of tobacco

In most of the studies that have analysed the effect of inhalation, the risk of bladder cancer was higher in inhalers than in non-inhalers, although the difference in most studies was less than 50% [reviewed in 22]. Results on smoking of filter-tipped versus untipped cigarettes are not consistent [reviewed in 22]. One characteristic of the descriptive epidemiology of bladder cancer is the high rate among men in countries where black (air-cured) tobacco cigarettes were common in the past (southern Europe, South America). Six studies have reported risk estimates by type of tobacco, and they consistently show a higher risk among smokers of black cigarettes compared with other smokers [Table VI]. The higher concentration

Table IV. Results of case-control studies on age at starting tobacco smoking and risk of urinary bladder cancer.

Reference	Country, gender	Age at starting smoking (years)	RR	95% CI
[23]	Canada, men	20+	1.6	1.1, 2.4
		15–19	2.3	1.6, 3.3
		<15	2.4	1.6, 3.6
	women	20+	1.5	0.9, 2.5
		15–19	2.7	1.4, 5.0
		<15	2.4	0.9, 6.4
[25]	France, men	31+	2.0	0.8, 5.0
		25–30	1.5	0.6, 3.4
		21–24	3.5	2.0, 6.4
		18–20	4.0	2.6, 6.2
		<18	4.9	3.1, 7.8
[26]	Italy, men and women	21+	1.8	0.9, 3.8
		<21	2.7	1.8, 4.1
[30]	Germany, men	21+	2.2	1.6, 3.2
		16–20	2.6	1.8, 3.6
		<16	6.2	3.4, 11
	women	21+	2.5	1.3, 5.0
		16–20	4.8	1.7, 13
		<16	1.6	0.2, 12
[32]	France, men	21+	4.6	2.0, 10
		17–20	4.9	2.6, 9.2
		13–16	5.4	2.8, 11
		<13	20	6.9, 60
[33]	UK, men	21+	2.0	1.4, 2.8
		17–20	1.9	1.4, 2.4
		7–16	2.3	1.7, 2.9
[34]	Germany, men	21+	5.2	0.9, 31
		16–20	5.7	1.0, 32
		<16	5.2	0.9, 31
	women	21+	2.4	0.6, 9.9
		<21	17	2.0, 137

RR = relative risk; CI = confidence interval.

Table V. Results of case–control studies on time since quitting tobacco smoking and risk of urinary bladder cancer.

Reference	Country, gender	Time since quitting smoking (years)	RR	95% CI
[37]	USA, men	1–3	2.6	1.6, 4.5
		4–6	2.9	1.7, 5.2
		7–9	1.5	0.8, 3.0
		10–12	1.6	0.8, 3.1
		13–15	1.2	0.6, 2.5
		16+	1.1	0.7, 1.8
[38]	UK, men	1–5	1.7	NA
		6–15	1.0	NA
		16–25	1.1	NA
		26–35	0.9	NA
[39]	Italy, men	<2	[5.8]	[3.6, 9.4]
		3–9	[3.0]	[1.6, 5.8]
		10–14	[2.2]	[0.9, 5.0]
		15+	[2.3]	[1.1, 4.8]
[23]	Canada, men	1–5	1.1	0.6, 1.9
		6–10	0.8	0.4, 1.7
		11+	1.4	0.7, 2.8
	women	1–5	0.4	0.2, 1.2
		6–10	0.7	0.1, 4.1
		11+	0.8	0.2, 3.7
[26]	Italy, men and women	2–4	3.1	1.6, 6.2
		5–14	1.8	1.0, 3.2
		15+	1.2	0.6, 2.5
[29]	Spain, men	<5	4.4	2.8, 7.0
		6–15	3.0	1.7, 5.2
		16+	2.4	1.3, 4.3
[30]	Germany, men	1–9	1.3	0.9, 1.8
		10–19	0.7	0.5, 1.0
		20+	0.6	0.4, 0.9
	women	1–9	0.8	0.3, 2.7
		10–19	1.7	0.4, 7.0
		20+	2.2	0.8, 6.3
[32]	France, men	<3	5.0	2.6, 9.7
		3–15	7.1	3.6, 14
		16+	4.6	2.3, 9.1
[33]	UK, men	1–9	1.9	1.4, 2.6
		10–19	1.5	1.1, 2.1
		20+	1.2	0.9, 1.7
[40]	Egypt, men	<10	5.8	1.6, 21
		10+	3.4	1.0, 11
[34]	Germany, men	1–9	3.4	1.6, 6.9
		10+	1.7	0.9, 3.0
[35]	USA, men	<10	2.3	1.8, 2.9
		10–19	1.9	1.5, 2.5
		20+	1.1	0.9, 1.5
	women	<10	2.7	1.5, 4.8
		10–19	1.1	0.6, 2.1
		20+	1.1	0.6, 2.0

Figures in square brackets = results obtained from raw data reported in the original publication.
RR = relative risk; CI = confidence interval; NA = not available.

of aromatic amines in black versus blond tobacco may explain the difference in carcinogenicity for the urinary bladder [42].

Smoking products other than cigarettes

Although several cohort and case–control studies addressed the risk of urinary bladder cancer for smoking of cigars and pipe, the number of exclusive cigar or pipe smokers was too small in most studies to provide stable risk estimates. The results of the largest available study, based on a pooled analysis of European case–control studies, are summarized in Table VII: they provide strong evidence of a carcinogenic effect of these products, which is comparable to that of cigarettes. No adequate data are available on the bladder carcinogenicity of other tobacco products (e.g. bidis).

Table VI. Results of case–control studies on type of tobacco and risk of urinary bladder cancer.

Reference	Country, gender	Type of tobacco	RR	95% CI
[39]	Italy, men	Blond	[1.7]	[0.8, 3.6]
		Black	[3.7]	[2.1, 6.5]
[25]	France, men	Blond	1.9	1.2, 2.9
		Mixed	3.0	1.6, 5.7
		Black	4.4	2.3, 8.3
[26]	Italy, men and women	Blond, mixed	2.7	1.8, 4.0
		Black	3.8	2.0, 7.4
[28]	Uruguay, men	Blond	1.0 [a]	–
		Mixed	2.4	1.0, 5.6
		Black	2.7	1.3, 5.4
[29]	Spain, men	Blond	3.2	1.5, 6.6
		Black	3.7	2.4, 5.8
[32]	France, men	Blond	3.1	1.3, 7.8
		Black	6.7	3.1, 10

Figures in square brackets = results obtained from raw data reported in the original publication.
[a] Reference category.
RR = relative risk; CI = confidence interval.

Effect on non-transitional cell bladder carcinoma

The great majority of bladder cancers in most populations are transitional cell carcinomas, and the results summarized above were based on series of cases including mainly this histological type. One pooled analysis of nine case–control studies from Europe, however, included 146 cases of non-transitional-cell bladder cancer and 727 controls [44]: the results, summarized in Table VIII, provide strong evidence of a carcinogenic effect of tobacco smoking on this type of bladder cancer. Studies conducted in populations with a high proportion of non-transitional-cell carcinomas, such as Egypt and Zimbabwe, also reported a positive association with tobacco smoking [40,45].

Table VII. Relative risk (RR) of urinary bladder cancer for smoking of cigars and pipe; results of a pooled analysis of 11 case–control studies of European men [43].

Smoking category	RR	95% CI
Pipe only		
Ever smoking	1.9	1.2, 3.1
1–39 years	1.4	0.7, 2.8
40+ years	2.5	1.3, 4.9
Cigar only		
Ever smoking	2.3	1.6, 3.5
1–29 years	1.4	0.8, 2.6
30–39 years	2.7	1.3, 5.7
40+ years	3.8	2.1, 7.1

CI = confidence interval.

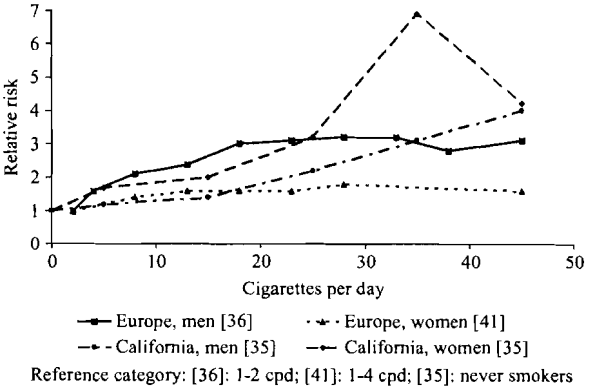
Table VIII. Relative risk (RR) of non-transitional-cell carcinoma of the urinary bladder for tobacco smoking; results of a pooled analysis of nine case–control studies of European men and women [44].

Smoking category	RR	95% CI
Current smokers		
0.06–21.51 pack-years	2.2	1.0, 4.8
21.52–40.51 pack-years	2.7	1.3, 5.6
40.52+ pack-years	7.0	3.6, 14
Ex-smokers		
0.06–21.51 pack-years	1.6	0.8, 3.0
21.52–40.51 pack-years	1.4	0.6, 3.3
40.52+ pack-years	1.6	0.7, 3.9

CI = confidence interval.

Interaction with gender and ethnicity

In most populations the incidence of bladder cancer is higher in men than women, and the majority of the risk estimates available in the literature refer to men (Table II and Table III). Results in women are



Reference category: [36]: 1-2 cpd; [41]: 1-4 cpd; [35]: never smokers

Figure 2. Relative risk of urinary bladder cancer for intensity of tobacco smoking in men and women.

Table IX. Relative risk (RR) of urinary bladder for exposure to involuntary smoke.

Reference	Country	Design	Exposure	RR	95% CI
[46]	USA	Ca/co	Spouse [a]	1.1	0.2, 7.6
[23]	Canada	Ca/co	Household	[0.80]	[0.49, 1.32]
			Workplace	[0.92]	[0.60, 1.44]
[47]	Netherlands	Cohort	Spouse, current	0.74	0.29, 1.9
			Spouse, former	0.95	0.46, 2.0
			Parents	1.2	0.56, 2.4
			Workplace	1.4	0.70, 2.6
			1–2 hours/day	0.69	0.33, 1.4
			3+ hours/day	0.64	0.29, 1.4

Figures in square brackets = results obtained from raw data reported in the original publication.
[a] Including smokers (RR adjusted for active smoking).
CI = confidence interval.

relatively sparse, and the differences that were observed in some studies can be attributed either to chance or to residual confounding (i.e. not taking into account the greater amount or duration of smoking among men compared with women). The results of the two most informative studies are summarized in Figure 2. In one study from California, which was specifically conducted to assess the effect of gender on the association between tobacco smoking and bladder cancer, the risk was higher among women than men, and the interaction between gender and smoking was statistically significant ($p = 0.016$) [35]. These authors also reported higher regression coefficients in women compared with men between haemoglobin adducts formed by tobacco-related aromatic amines and amount of smoking, thus suggesting a stronger carcinogenicity of tobacco in the former group. However, these results were not confirmed by a pooled analysis of case–control studies from Europe [36,41] and by the recent meta-analysis [4] (Table I). Several studies have addressed the possible effect of race or ethnicity on the association between tobacco smoking and urinary bladder cancer [22]: the differences in the results are compatible with chance variation (Table I).

Involuntary exposure to tobacco smoke

Two case–control and one cohort study have investigated the risk of bladder cancer with involuntary exposure to tobacco smoke [23,46,47]. Their results are summarized in Table IX. Overall, there is no evidence of an increased risk, but the results are fairly imprecise.

Use of smokeless tobacco products

Several studies have reported estimates of bladder cancer risk for use of smokeless tobacco products (tobacco chewing or snuff). In only six of them, however, was the analysis either restricted to never-smokers or properly adjusted for the potential confounding effect of active smoking [23,35,48–51]. The relevant results are summarized in Table X. In one study there was a suggestion of an increased risk of bladder cancer among chewers or snuff users, but the risk estimates were compatible with no effect. In the remaining studies, no association was observed. Although the database is somewhat limited, it can be concluded that there is no consistent evidence of an association between use of smokeless tobacco products and bladder cancer risk.

Table X. Relative risk (RR) of urinary bladder for use of smokeless tobacco products.

Reference	Country	Inclusion of smokers[a]	Exposure	RR	95% CI
[48]	Canada	Yes	Chewing	0.9	0.5, 1.6
[49]	Denmark	Yes	Chewing	1.59	NA
[50]	USA	No	Chewing	1.02	0.67, 1.54
			Snuff	0.77	0.38, 1.56
[51]	USA	No	Chewing	[2.78]	[0.38, 20.2]
			Snuff	[2.73]	[0.48, 15.6]
[23]	Canada	Yes	Chewing	0.47	0.21, 1.07
			Snuff	0.60	0.34, 1.06
[35]	USA	No	Smokeless tobacco	0.4	0.05, 3.3

Figures in square brackets = results obtained from raw data reported in the original publication.
[a] RR adjusted for smoking in studies including smokers.
CI = confidence interval; NA = not available.

Conclusions

The proportion of bladder cancers attributable to tobacco smoking varies among countries, based on the maturity of the tobacco epidemics. In the pooled analysis of European case–control studies, it was estimated that 66% of cases in men (95% CI 61%, 70%) and 30% of cases in women (95% CI 25%, 35%) were attributable to this habit [36,41]. The lower proportion in women than in men is explained by the earlier stage of the tobacco-related epidemic among European women, and it is likely to increase in the future. In other countries, different estimates would be obtained, but tobacco smoking remains the single most important cause of bladder cancer in most human populations.

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