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ORIGINAL PAPER

A pooled analysis of bladder cancer case–control studies evaluating smoking in men and women

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Abstract
Objective A recent study suggested that risk of bladder cancer may be higher in women than in men who smoked comparable amounts of cigarettes. We pooled primary data from 14 case–control studies of bladder cancer from Europe and North America and evaluated differences in risk of smoking by gender.

Methods The pooled analysis included 8316 cases (21% women) and 17,406 controls (28% women) aged 30–79 years. Odds ratios (ORs) and 95% confidence intervals (95% CI) for smoking were adjusted for age and study. Exposure-response was evaluated in a stratified analysis by gender and by generalized additive models.

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Results The odds ratios for current smokers compared to nonsmokers were 3.9 (95% CI 3.5–4.3) for males and 3.6 (3.1–4.1) for females. In 11 out of 14 studies, ORs were slightly higher in men. ORs for current smoking were similar for men (OR = 3.4) and women (OR = 3.7) in North America, while in Europe men (OR = 5.3) had higher ORs than women (OR = 3.9). ORs increased with duration and intensity in both genders and the exposure-response patterns were remarkably similar between genders.

Conclusion These results do not support the hypothesis that women have a higher relative risk of smoking-related bladder cancer than men.

Keywords Bladder cancer · Case–control studies · Gender differences · Pooled analysis · Tobacco smoke

Introduction

Cigarette smoking is the most important risk factor for bladder cancer causing around 50–65% of male cases and 20–30% of female cases [1–3]. Black tobacco conveys a higher risk compared to blond tobacco, while other smoking characteristics such as the use of filters have not been consistently associated with differences in risk. Some studies on lung cancer have suggested that women may be more susceptible to tobacco carcinogens than men [4–6] although most studies and in particular large cohort studies, have not found gender differences in smoking and lung cancer [7–9]. In a recent study on bladder cancer [10], women who smoked had higher levels of 3- and 4-aminobiphenyl (ABP)-hemoglobin adducts than men smoking equal amounts of cigarettes. 4-ABP, an aromatic amine, is believed to be a major bladder carcinogen in tobacco smoke. The odds ratios for heavy smoking and bladder cancer in that study were higher among women than in men. It was noted, however, that the pattern for absolute risks was the opposite since incidence rates for bladder cancer are much higher among men [11]. Gender differences in bladder cancer in relation to smoking have been explored in only few studies mainly due to the small number of women enrolled in most studies, and results are inconsistent [12–16].

We pooled data from 14 case–control studies on bladder cancer from Europe and North America and evaluated differences in bladder cancer risk between genders by smoking. The case–control studies were previously pooled for analyses evaluating occupation [17] and exposure to disinfection by-products in drinking water [18].

Methods

The 14 studies included in the pooled analysis were conducted between 1976 and 1996 and comprised three studies from Germany [19–21], two from Spain [22–24], Italy [25, 26], USA [27, 28], and France [14, 29, 30], and one each from Greece [31], Denmark [32] and Canada [33]. Criteria for inclusion of the studies in the two previous pooled analyses were the availability of detailed information on occupational exposures in studies conducted in European Union countries [17] and of individual exposure estimates to disinfection by-products in studies in Europe or North America [18]. The original pooled analysis on disinfection by-products included also a study from Finland [34], which did not have detailed information on all the smoking-related variables used in this analysis. The pooled analysis on disinfection byproducts included only part [35] of the US NCI National bladder cancer study population (only whites) that is included in this analysis on smoking [27]. All studies were performed after approval by a local institutional review board.

In the pooled data set, we excluded subjects less than 30 years of age and greater than 79 years of age (1209 subjects outside this age range) so as to apply similar selection criteria in all studies. We also excluded 560 European cases and 74 North American cases interviewed more than 2 years after diagnosis. The final analysis included 8316 cases (21% women) and 17406 controls (28% women) (Table 1). Six studies had population controls [21, 24, 27, 28, 32, 33], one [23] both hospital and population controls and the rest had hospital controls [19, 20, 25, 26, 29–31]. The diagnoses of the hospital controls by study included: urological controls [19, 20, 26], osteoarticular, digestive and heart diseases [29], various diseases other than cancer [30], urological and surgical controls [25], various diagnoses excluding urological and heart diseases, cancers of the respiratory system and digestive system [23], and traumas [31]. Controls were individually or frequency-matched to cases on gender, age (within 5 years), and geographic area. The largest country component was from the National Bladder Cancer Study, USA [27] with 31% of all cases and 27% of all controls. The case: control ratio differed per study, ranging from 1:1 to 1:4.5. The mean age of cases was 64 years (median 65 years) compared to 63 in controls (median 64 years). For cases 82% had ever smoked compared to 64% for controls. All patients recruited in the case series were histologically confirmed. Two studies [19, 20] also included cases of the ureter and urethra.

Primary data from the 14 studies were combined using common coding and classification schemes for all

Table 1 Bladder cancer cases and controls included in the pooled analysis by study, gender, age and smoking status

Studies (ref, publication year)	Cases		Controls	
	Number	%	Number	%
Canada [33, 1996]	696	8.4	1545	8.9
Denmark [32, 1987]	376	4.5	747	4.3
France 1[29, 1993]	633	7.6	717	4.1
France 2 [30, 1994]	115	1.4	232	1.3
Germany 1[19, 1988]	458	5.5	581	3.3
Germany 2 [20, 1999]	259	3.1	280	1.6
Germany 3 [21, 2000]	684	8.2	3732	21.4
Greece [31, 1985]	277	3.3	279	1.6
Italy 1[25, 1985]	418	5.0	729	4.2
Italy 2 [26, 1996]	155	1.9	532	3.1
Spain 1[23, 1989]	441	5.3	1055	6.1
Spain 2 [24, 2000]	184	2.2	293	1.7
USA 1 [28, 1998]	1032	12.4	1923	11.1
USA 2 [27, 1987]	2588	31.1	4761	27.3
Gender				
Men	6587	79.2	12536	72.0
Women	1729	20.8	4870	28.0
Age				
30–39 y	118	1.4	454	2.6
40–49 y	515	6.2	1445	8.3
50–59 y	1742	21.0	4152	23.9
60–69 y	3183	38.3	6146	35.3
70–79 y	2758	33.1	5209	29.9
Smoking				
No smokers	1455	17.5	6234	35.8
Ex smokers	2978	35.8	6120	35.2
Current smokers	3631	43.7	4732	27.2
Unknown	252	3.0	320	1.8
All	8316		17406	

variables. We extracted from the original databases information on exposure and potential confounders: age, gender, study, smoking status (never smokers; ex-smokers and current smokers), duration of smoking, average number of cigarettes smoked per day, pack-years, and occupation. Ex-smokers were defined as those cases who gave up smoking one or more years before the interview. Most analyses were restricted to current smokers because information of age at cessation was not available in all studies for former smokers. Information on occupation was available for 13 studies, and we used a common definition for ever having worked in a priori defined high-risk occupations, such as textile workers, painters, metal workers, mechanics, rubber workers, motor vehicle drivers, chemical workers and hairdressers [17].

We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CI) for the different exposure indices separately by gender. Tests of statistical significance were two-sided ($p < 0.05$). All ORs were adjusted by study (14 studies) and age (10 categories). The pattern of the exposure-response relationship was first evaluated through a stratified analysis by gender, and differences in gender-specific ORs were evaluated through an interaction term between gender and the smoking exposure index. We then examined exposure response for cigarette smoking (duration, intensity) as continuous variables fitting linear, quadratic and cubic terms in the general linear model. Finally we examined exposure response through a generalized additive model using a natural spline for the continuous smoking variables applying 2 or 3 degrees of freedom, depending on the fit of each variable as examined through the Akaike Information Criterion-AIC. This smoothing method allows an evaluation of the pattern of the exposure-response curve without constraints from arbitrarily defined exposure categories. This comparison between exposure response in men and women was done for the exposure range for which a sufficiently large number of cases and controls were available in women, since the exposure range was narrower in women than in men. Adjusted ORs were calculated for the main effects within individual studies and the heterogeneity of effects among studies was evaluated through a meta-analysis [36] and through graphical methods [37]. In the presence of heterogeneity both fixed and random effects models were applied. Analyses were performed using the statistical packages STATA v.8.0 and S-Plus 2000.

Results

Smoking prevalence among controls differed substantially between studies in women, while differences between studies in men were smaller (Table 2). In women, smoking was more frequent in study centers in North America and northern Europe with prevalence above 30%, and was lowest in southern Europe with prevalence below 10% in most studies. Prevalence of smoking increased in women in recent years and this was reflected in differences in the proportion of smokers between studies of the same country such as Spain and Germany. The average duration of smoking was 40.1 years (sd = 12.2) in men and 34.1 years (sd = 12.7) in women. The average intensity of smoking was 20.9 cigarettes per day (sd = 11.5) in men and 17.1 cigarettes per day (sd = 9.5) in women.

The odds ratio for male current smokers compared to male never-smokers was 3.89 (95% CI 3.53–4.29) (Table 3). This was slightly higher than that of female current smokers compared to female never-smokers (OR = 3.55, 95% CI 3.06–4.10). The p-value for the interaction term between current smoking and gender was 0.002. ORs increased with increasing duration, intensity (cigarettes per day) and pack-years (not shown) in both

Table 2 Number of controls and percentage of ever smokers by study and gender and type of control

Studies (ref)	Men		Women		Control
	Number	% ever smokers	Number	% ever smokers	
Canada [33]	973	73	572	50	population
Denmark [32]	560	83	187	56	population
France 1 [29]	616	78	101	17	hospital
France 2 [30]	194	71	38	5	hospital
Germany 1 [19]	461	81	120	17	hospital
Germany 2 [20]	225	76	55	16	hospital
Germany 3 [21]	2342	77	1390	36	population
Greece [31]	235	74	44	5	hospital
Italy 1 [25]	546	83	183	30	hospital
Italy 2 [26]	369	69	163	26	hospital
Spain 1 [23]	937	79	118	6	both
Spain 2 [24]	275	77	18	17	population
USA1 [28]	1248	68	675	34	population
USA2 [27]	3555	71	1206	38	population
All	12536	74	4870	36	

Table 3 Odds ratios for cigarette smoking and bladder cancer by gender

Variables	Male			Female		
	No. case/control	OR[a]	95% CI	No. case/control	OR[a]	95% CI
Smoke status						
Never	697/3136	1.00		758/3098	1.00	
Ex	2669/5381	2.21	2.01–2.43	309/739	2.21	1.87–2.61
Current	3020/3759	3.89	3.53–4.29	611/973	3.55	3.06–4.10
Duration in years[b]						
Never	697/3136	1.00		758/3098	1.00	
1–<10	12/46	1.44	0.74–2.78	10/37	1.49	0.71–3.14
10–<20	63/191	1.88	1.33–2.66	28/100	1.88	1.14–3.08
20–<30	237/434	2.89	2.33–3.60	87/193	3.01	2.21–4.09
30–<40	728/959	4.00	3.44–4.65	170/294	3.29	2.61–4.17
40–<50	1052/1156	4.48	3.94–5.11	227/236	4.76	3.81–5.94
≥50	827/856	3.98	3.47–4.56	85/111	3.48	2.54–4.77
p-value[c]			<0.0001			<0.0001
No. cigarettes/day[b]						
Never	697/3136	1.00		758/3098	1.00	
0.2–<10	209/422	2.26	1.86–2.74	84/200	2.35	1.76–3.13
10–<20	876/1190	3.78	3.32–4.30	204/346	3.51	2.85–4.34
20–<30	1093/1259	4.19	3.71–4.73	229/312	4.11	3.33–5.08
30–<40	363/373	4.77	4.01–5.66	53/66	4.30	2.91–6.36
≥40	339/341	4.67	3.91–5.58	38/44	5.04	3.16–8.06
p-value[c]			<0.0001			<0.0001

[a] OR (95% CI) are adjusted by age and study

[b] Ex-smokers were excluded from the analyses by duration and intensity. 357 cases and 439 controls have missing information on duration. 395 cases and 499 controls have missing information on number of cigarettes per day

[c] *p*-value for linear trend

Table 4 Odds ratios and 95% confidence intervals for the joint effects of intensity (cigarettes per day) and duration of smoking by gender

No. cigarettes/day	Number of years smoking					
	Men			Women		
	<20 y	20–39 y	≥40 y	<20 y	20–39 y	≥40 y
<20						
No. cases/No. controls	36/122	327/619	719/864	25/94	107/274	154/178
OR (95% CI)[a]	2.09 (1.36–3.21)	3.24 (2.68–3.92)	3.69 (3.19–4.25)	1.72 (1.04–2.84)	2.35 (1.80–3.07)	4.32 (3.37–5.53)
20–<30						
No. cases/No. controls	25/69	362/455	699/729	10/30	102/147	116/135
OR (95% CI)[a]	2.33 (1.38–3.92)	4.55 (3.76–5.51)	4.09 (3.55–4.71)	2.36 (1.06–5.26)	4.20 (3.10–5.67)	4.07 (3.08–5.39)
≥30						
No. cases/No. controls	12/37	261/296	426/380	3/12	47/64	41/34
OR (95% CI)[a]	1.93 (0.95–3.92)	4.65 (3.76–5.76)	4.78 (4.04–5.66)	1.44 (0.41–5.84)	4.19 (2.75–6.39)	5.25 (3.25–8.48)

Analysis limited to current smokers compared to never-smokers (non-exposed)

[a] OR (95% CI) adjusted for age and study

men and women (Table 3). Tests for linear trend were in all occasions statistically significant, although ORs for intensity and pack-years (not shown) tended to plateau at high exposure levels. ORs for duration and intensity of smoking categories were very similar between genders. Results are not presented for models including both intensity and duration because there is a high degree of colinearity between these two variables and some strata were dropped when adjusting one variable for the other. Given that the dose response is not linear (see below) we could not evaluate mutual confounding by fitting single continuous variables for intensity and duration. An interaction term between smoking and gender was statistically significant for duration of smoking (p-value = 0.007) while it was not significant for intensity (p-value = 0.121).

Table 4 shows the ORs for the cross-classification of smoking intensity and duration by gender, for the same categories as those reported by Castelao et al. [10]. By contrast to Castelao et al. who examined ever versus never smokers, we examined current versus never smokers, since quitting smoking may show different patterns by gender. ORs were very similar between genders in most exposure cells. A higher OR was observed in women (OR = 5.25, 95% CI=3.25–8.48) than in men (OR = 4.78, 95% CI=4.04–5.66) in the extreme cigarette smoking cell of 30 or more cigarettes smoked per day for a duration of 40 or more years. The confidence intervals, particularly for women, were wide, and an interaction term between this highest category of smoking and gender was not statistically significant (p-value = 0.852).

Exposure-response patterns were examined through general additive models (GAM) among current smokers versus never smokers for pack-years (Fig. 1), intensity, and duration of smoking (not shown) and were remarkably similar between genders. In both genders, the rate of increase in risk was higher in the lower exposure

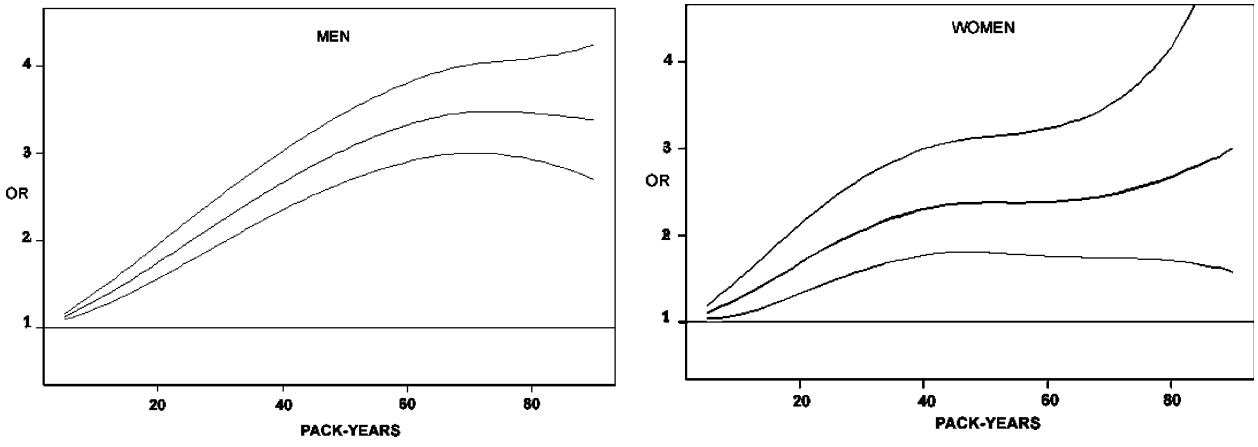

Fig. 1 Odds Ratios (bold line) and 95% confidence interval (light lines) for pack-years and bladder cancer among current smokers versus never smokers using a generalized additive model with a natural spline (3 degrees of freedom) for men and women. The spline is adjusted for age and center. Analysis limited to subjects with consumption less than 90 pack-years

levels as compared to higher exposures. The ORs at high exposures are less stable due to small numbers and the confidence intervals are wider. An analysis examining cigarette smoking as a continuous variable using general linear models (GLM) also showed very similar exposure patterns. A cubic model was the best fit for intensity of smoking (cigarettes per day) in both men and women. The estimated parameters (betas) in men were 0.149 (standard error 0.011) for the linear term, −0.0048 (se 0.0007) for the quadratic term and 0.00005 (se 0.00001) for the cubic term. In women the betas were 0.157 (se 0.02), −0.0055 (se 0.0014) and 0.00006 (se 0.00002) respectively. For duration (per year smoking) a quadratic model was the best fit in both men and women. The estimated parameters in men were 0.065 (se 0.005) for the linear term and −0.0007 (se 0.0001) for the quadratic. The corresponding estimates for women were 0.059 (se 0.009) and −0.0006 (se 0.0002). Finally, a cubic model was the best fit for pack-years in both men and women. The estimated parameters in men were 0.076 (se 0.007) for the linear term, −0.0013 (se 0.0002) for the quadratic and 0.000007 (se 0.000002) for the cubic. In women the corresponding parameters were 0.104 (se 0.011), −0.0023 (se 0.0004), and 0.00002 (se 0.000004).

ORs for current smokers versus never smokers were slightly higher in men than in women in 11 out of 14 studies (Fig. 2). An analysis by wide geographic areas indicated that ORs for current smokers compared to never smokers were similar for men (OR = 3.37, 2.81–4.04) and women (OR = 3.72, 2.61–5.29) in North America, while European men (OR = 5.31, 4.14–6.80) tended to have higher ORs than European women (OR = 3.87, 2.98–5.03). Within Europe, differences by gender were not consistently greater for southern European countries where black tobacco had been traditionally smoked more than in other areas (Fig. 2). No statistically significant heterogeneity between studies was present for women (Q-statistic = 15.3; 13 degrees of freedom, p-value = 0.288). There was heterogeneity among men (Q-statistic = 38.6; 13 degrees of freedom, p-value < 0.001) mainly due to the lower ORs (current smokers versus never smokers) observed in studies in North America and particularly the US NCI study [27], and also the higher ORs observed in the two smallest studies in southern Europe [24, 26]. The fixed effects model estimate from the meta-analysis was 3.78 (95% CI 3.43–4.18) while the random effects model was 4.61 (95% CI 3.8–5.6) due to the higher weight given in this model on smaller studies. Inclusion of the study by Castelao et al. [10] through a meta-analysis did not modify results. The fixed effects meta-analysis for men gave a meta-OR for current versus never smokers of 3.78 (3.43–4.18) without the study by Castelao et al. [10] and a meta-OR for current versus never smokers of 3.80 (3.46–4.17) with that study.

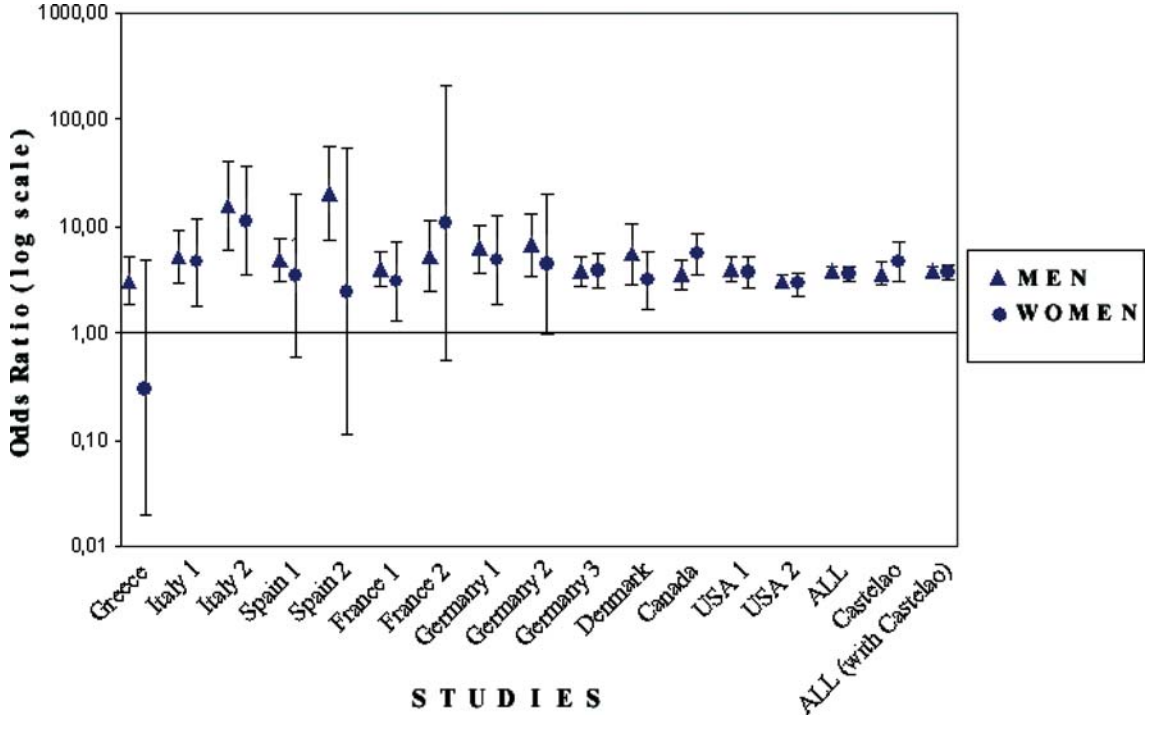

Fig. 2 Odds Ratios and 95% CI (vertical lines) for current smokers compared to never smokers for each study included in the pooled analysis, for all studies combined (fixed effects), for the study by Castelao et al. [10] and for all studies including the study by Castelao, by gender. Studies are ranked by wide geographical area: Southern Europe, Northern Europe and North America

In women, the meta-OR for current versus never smokers was 3.54 (3.06–4.11) without the study by Castelao et al. [10] and 3.66 (3.18–4.22) when adding that study.

ORs for studies using hospital controls (only European studies) were higher than for those using population controls (mostly North American studies). ORs for current versus never smokers based on hospital controls were 5.24 (3.85–7.11) in men and 4.48 (2.69–7.44) in women. ORs for current compared to never smokers based on population controls were 4.06 (3.12–5.31) for men and 3.57 (2.91–4.38) for women. Adjustment for employment in high risk occupations in the 13 studies that included this information (1470 exposed cases and 2965 exposed controls, OR for high risk occupation=1.16, 95% CI 1.07–1.27) did not modify substantially the odds ratios for current smokers compared to never smokers. Comparable occupational information was not available for one study [27]. The OR for men in these 13 studies was 4.51 (95% CI 3.97–5.13) without adjustment and 4.46 (95% CI 3.92–5.06) with occupation included in the model. For women the corresponding ORs were 3.72 (95% CI 3.04–4.55) and 3.75 (95% CI 3.06–4.59). Differences between genders for current smoking versus never smokers were slightly wider for subjects below age 50 with an OR for men of 4.07 (95% CI 2.95–5.63) and for women of 3.12 (95% CI 1.90–5.14). ORs for subjects above age 50 were 3.90 (95% CI 3.51–4.33) for men and 3.63 (95% CI 3.11–4.24) for women. Relative risks by gender were fairly similar irrespective of whether the study was done in the 1980s or in the 1990s, a period during which tar and other carcinogenic levels in cigarettes changed.

Discussion

Cigarette smoking is well established as a cause of bladder cancer, and smokers have two to three times the risk of non-smokers [1, 2]. Our results indicate that the risk of bladder cancer increases with duration and intensity of smoking and, as previously noted [38], there appears a plateau in risk at high exposure levels. In this pooled analysis the ORs were fairly equal for men and women. Small differences between genders were observed in specific exposure cells but the pattern of exposure-response was similar.

Differences in smoking-related risks between genders could occur because of varying patterns of cigarette smoking such as smoking black versus blond tobacco, filter cigarettes, inhalation practices, or because of the effect of age at initiation [39]. Smoking black tobacco has been shown to convey a higher risk for bladder cancer than blond tobacco, while other smoking patterns are associated with small, if any, differences in cancer risk [1, 2]. This information was not available for the present analysis, but an analysis by geographical region did not indicate higher odds ratios in studies in southern Europe where black tobacco has been smoked more.

The universally higher incidence of bladder cancer in men compared to women [40] has partly been attributed to smoking and occupation [16]. Adjustment for occupation affected results for smoking minimally in this pooled analysis. It has been suggested that the higher incidence in men could also be attributed to gender differences in environmental and dietary exposures or in differences in innate characteristics such as anatomic differences, urination habits or an effect of hormones, particularly androgens on tumor development [16]. There is little empirical evidence in humans of the potential mediating effect of hormones on smoking-related cancer risk. Information on menopausal status was not available in the pooled data, but a wider difference in risk between genders was observed in subjects below 50 years of age as compared to those above that age.

This pooled analysis was based on two existing international data sets [17, 18] and includes a large component of all populations evaluated for bladder cancer and nearly all countries where such studies have been conducted. It is unlikely that these results would be substantially modified by the addition of more studies. Pooling results of different studies conveys a considerable advantage by increasing the power of the study and also by verifying the presence of similar risks in different populations. There are, however, complexities concerning the methodology to be used and also the interpretation of the findings of pooled studies due to the differences between studies in the design and also in the prevalence of other risk factors. For example, the higher ORs found for studies using hospital controls compared to those using population controls was unexpected. If anything, hospital-based studies would be expected to have lower point estimates for smoking because of an anticipated higher prevalence rate of smoking among these controls compared to population-based controls. These differences are likely to be due to geographical differences, since hospital-based studies were only European, while those using population controls were mostly North American. The overall pattern in risk by gender between studies was consistent, although odds ratios for some of the smaller studies were unstable due to small numbers.

Differences in the two measures of risk, relative risk and absolute risk, may have led to different interpretations of results from studies that evaluate gender differences in cancer risk in relation to smoking [11]. While relative risks were higher in women in the study by Castelao et al. [10], absolute risks were higher in men [11]. In this pooled analysis, relative risks tended to be similar in men and women. Since incidence of bladder cancer is higher in men

in all base populations included in this pooled analysis [40], absolute risks are also higher in men.

It has been postulated that females may have a higher risk of smoking-related cancer than men, and that for the same amount of cigarettes smoked their risk for lung [4–6, 41] and bladder cancer [10] could be higher than that of men. Most studies on lung cancer and in particular cohort studies have not found, however, higher smoking-related risks among women [7–9, 42]. Some evidence of a differential effect has been found in studies evaluating intermediate endpoints. Lung cancer studies have suggested that formation of aromatic DNA adducts (mainly PAH adducts) is higher in women than in men, and that expression of CYP1A1, which is involved in the metabolism of PAHs, is higher in the lung epithelium of women compared to men [5, 6, 43]. Hormones could be involved in the higher expression of CYP1A1 in women [41]. In a study on lung cancer, women were shown to have lower DNA repair capacity than men [44]. In another study the effect of the GSTM1 null genotype in relation to lung cancer was greatest in female smokers [45]. It has been hypothesized that the greater susceptibility of women to smoking and development of lung cancer may have its origins in puberty due to the differential age development of the lungs in boys and girls [39]. Only some of the proposed mechanisms concerning a greater susceptibility of women for smoking and lung cancer are relevant for bladder cancer. The most comprehensive meta-analysis of GSTM1 and bladder cancer did not examine gender differences [46]. A recent study evaluating 4-ABP-haemoglobin adducts found that women who smoked had higher levels of adducts than men [10], indicating that some women may be at higher risk for developing tobacco-related cancers. In that study, however, the ORs for smoking and bladder cancer among men and women were similar in most exposure cells. It is unclear why ABP-adducts formed at a much higher rate in women than in men who smoked comparable amounts while a similar pattern was not consistently observed for bladder cancer risk in the same study.

In conclusion, the results of this pooled analysis that includes a large population sample from Western Europe and North America show that the relative risk for smoking and bladder cancer are similar in both genders. These results do not support the hypothesis of an increased risk of smoking-related bladder cancer among women. Given the similar genetic origins of the studied base populations [47], the relatively small differences of smoking-related bladder cancer risk by gender reported in specific studies are likely to be due to chance.

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References

1. Kogevinas M, Trichopoulos D (2000) Urinary bladder cancer. In: Adami HO, Hunter D, Trichopoulos D (eds) Textbook of Cancer Epidemiology 1st ed. Oxford University Press, New York, pp 446–466
2. Silverman D, Morrison A, Devesa S (1996) Bladder cancer In: Schottenfeld D, Fraumeni J (eds) Cancer Epidemiology and Prevention. 2nd edn. Oxford University Press, New York, pp 1156–1179
3. Brennan P, Bogillot O, Greiser E, et al. (2001) The contribution of cigarette smoking to bladder cancer in women (pooled European data). Cancer Cause Control 12:411–417
4. Risch HA, Howe GR, Jain M, Burch JD, Holowaty EJ, Miller AB (1993) Are female smokers at higher risk for lung cancer than male smokers? A case–control analysis by histologic type. Am J Epidemiol 138:281–293
5. Ryberg D, Hewer A, Phillips DH, Haugen A (1994) Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. Cancer Res 54:5801–5803
6. Zang EA, Wynder EL (1996) Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst 88:183–192
7. Agudo A, Ahrens W, Benhamou E, et al. (2000) Lung cancer and cigarette smoking in women: a multicenter case–control study in Europe. Int J Cancer 88:820–827
8. Vineis P, Alavanja M, Buffler P, et al. (2004) Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst 96:99–106
9. Bain C, Feskanich D, Speizer FE, et al. (2004) Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst 96:826–834
10. Castelao JE, Yuan JM, Skipper PL, et al. (2001) Gender- and smoking-related bladder cancer risk. J Natl Cancer Inst 93:538–545
11. Perneger TV (2001) Sex, smoking, and cancer: a reappraisal. J Natl Cancer Inst 93:1600–1602
12. Howe GR, Burch JD, Miller AB, et al. (1980) Tobacco use, occupation, coffee, various nutrients, and bladder cancer. J Natl Cancer Inst 64:701–713
13. Morrison AS, Buring JE, Verhoek WG, et al. (1984) An international study of smoking and bladder cancer. J Urol 131:650–654
14. Clavel J, Cordier S, Boccon-Gibod L, Hemon D (1989) Tobacco and bladder cancer in males: increased risk for inhalers and smokers of black tobacco. Int J Cancer 44:605–610
15. Augustine A, Hebert JR, Kabat GC, Wynder EL (1988) Bladder cancer in relation to cigarette smoking. Cancer Res 48:4405–4408
16. Hartge P, Harvey EB, Linehan WM, et al. (1990) Unexplained excess risk of bladder cancer in men. J Natl Cancer Inst 82:1636–1640
17. Kogevinas M, 't Mannetje A, Cordier S, et al. (2003) Occupation and bladder cancer among men in Western Europe. Cancer Cause Control 14:907–914

18. Villanueva CM, Cantor KP, Cordier S, et al. (2004) Disinfection by-products and bladder cancer: a pooled analysis. Epidemiology 15:357–367
19. Claude JC, Frentzel-Beyme RR, Kunze E (1988) Occupation and risk of cancer of the lower urinary tract among men. A case–control study. Int J Cancer 41:371–379
20. Pohlabeln H, Jöckel KH, Bolm-Audorff U (1999) Non-occupational risk factors for cancer of the lower urinary tract in Germany. Eur J Epidemiol 15:411–419
21. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W (2000) Occupational risk factors for urothelial carcinoma: agent-specific results from a case–control study in Germany. MURC Study Group. Int J Epidemiol 29:238–247
22. Lopez-Abente G, Gonzalez CA, Errezola M, et al. (1991) Tobacco smoke inhalation pattern, tobacco type, and bladder cancer in Spain. Am J Epidemiol 134:830–839
23. Gonzalez CA, Lopez-Abente G, Errezola M, et al. (1989) Occupation and bladder cancer in Spain: a multi-centre case–control study. Int J Epidemiol 18:569–577
24. Serra C, Bonfill X, Sunyer J, et al. (2000) A case–control study on bladder cancer and the textile industry. Scand J Work Environ Health 26:476–481
25. Vineis P, Magnani C, (1985) Occupation and bladder cancer in males: a case–control study. Int J Cancer 35:599–606
26. Porru S, Aulenti V, Donato F, et al. (1996) Bladder cancer and occupation: a case–control study in northern Italy. Occup Environ Med 53:6–10
27. Hartge P, Silverman D, Hoover R, et al. (1987) Changing cigarette habits and bladder cancer risk: a case–control study. J Natl Cancer Inst 78:1119–1125
28. Cantor KP, Lynch CF, Hildesheim ME, et al. (1998) Drinking water source and chlorination byproducts. I. Risk of bladder cancer Epidemiology 9:21–28
29. Cordier S, Clavel J, Limasset JC, et al. (1993) Occupational risks of bladder cancer in France: a multicentre case–control study. Int J Epidemiol 22:403–411
30. Hours M, Dananche B, Fevotte J, et al. (1994) Bladder cancer and occupational exposures. Scand J Work Environ Health 20:322–330
31. Rebelakos A, Trichopoulos D, Tzonou A, Zavitsanos X, Velonakis E, Trichopoulos A (1985) Tobacco smoking, coffee drinking, and occupation as risk factors for bladder cancer in Greece. J Natl Cancer Inst 75:455–461
32. Jensen OM, Wahrendorf J, Blettner M, Knudsen JB, Sorensen BL (1987) The Copenhagen case–control study of bladder cancer: role of smoking in invasive and non-invasive bladder tumours. J Epidemiol Community Health 41:30–36
33. King WD, Marrett LD (1996) Case–control study of bladder cancer and chlorination by-products in treated water (Ontario, Canada). Cancer Cause Control 7:596–604
34. Koivusalo M, Hakulinen T, Vartiainen T, Pukkala E, Jaakkola JJ, Tuomisto J (1998) Drinking water mutagenicity and urinary tract cancers: a population-based case–control study in Finland. Am J Epidemiol 148:704–712
35. Lynch CF, Woolson RF, O'Gorman T, Cantor KP (1989) Chlorinated drinking water and bladder cancer: effect of misclassification on risk estimates. Arch Environ Health 44:252–259
36. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials-Control. Clin Trials 7:177–188
37. Galbraith RF (1988) A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 7:889–894
38. Vineis P, Kogevinas M, Simonato L, Brennan P, Boffetta P (2000) Levelling-off of the risk of lung and bladder cancer in heavy smokers: an analysis based on multicentric case–control studies and a metabolic interpretation. Mutat Res 463:103–110
39. Wiencke JK, Kelsey KT (2002) Teen smoking, field cancerization, and a ''critical period'' hypothesis for lung cancer susceptibility. Health Perspect 110:555–558
40. Ferlay J, Bray F, Pisani P, Parkin DM (2001) GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC CancerBase No. 5, IARC Press, Lyon
41. Haugen A (2002) Women who smoke: are women more susceptible to tobacco-induced lung cancer? Carcinogenesis 23:227–229
42. Blot WJ, McLaughlin JK (2004) Are women more susceptible to lung cancer? J Natl Cancer Inst 96:812–813
43. Mollerup S, Ryberg D, Hewer A, Phillips DH, Haugen A (1999) Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients. Cancer Res 59:3317–3320
44. Wei Q, Cheng L, Amos CI, et al. (2000) Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst 92:1764–1772
45. Tang DL, Rundle A, Warburton D, et al. (1998) Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. Carcinogenesis 19:1949–1953
46. Engel LS, Taioli E, Pfeiffer R, et al. (2002) Pooled analysis and meta-analysis of glutathione S-transferase M1 and bladder cancer: a HuGE review. Am J Epidemiol 156:95–109
47. Cavalli-Sforza LL, Bodmer WF (1971) The Genetics of Human Populations, 1st edn. Dover Publications, INC. Mineola, New York