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The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks

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Abstract

Context: Tobacco smoke includes a mix of carcinogens implicated in the etiology of bladder cancer (BC) and renal cell cancer (RCC).
Objective: We reviewed the impact of tobacco exposure on BCC and RCC incidence and mortality, and whether smoking cessation decreases the risk.
Evidence acquisition: A systematic review of original articles in English was performed in August 2013. Meta-analysis of risks was performed using adjusted risk ratios where available. Publication bias was assessed using Begg and Egger tests.
Evidence synthesis: We identified 2683 papers, of which 114 fulfilled our inclusion criteria, of which 90 studies investigated BC and 24 investigated RCC. The pooled relative risk (RR) of BC incidence was 2.57 (95% confidence interval [CI] 2.37–2.78) for all smokers, 3.37 (3.01–3.78) for current smokers, and 1.98 (1.76–2.22) for former smokers. The corresponding pooled RR of BC disease-specific mortality (DSM) was 1.79 (1.40–2.29), 1.89 (1.29–2.78) and 1.66 (1.10–2.52). The pooled RR of RCC incidence was 1.27 (1.18–135) for all smokers, 1.29 (1.14–1.46) for current smokers, and 1.14 (1.06–1.22) for former smokers. The corresponding RCC DSM risk was 1.20 (1.02–1.41), 1.32 (1.08–1.62), and 1.01 (0.85–1.18).
Conclusions: We present an up-to-date review of tobacco smoking and BC and RCC incidence and mortality. Tobacco smoking significantly increases the risk of BC and RCC incidence. BC incidence and DSM risk are greatest in current smokers and lowest in former smokers, indicating that smoking cessation confers benefit. We found that secondhand smoke exposure is associated with a significant increase in BC risk.
Patient summary: Tobacco smoking affects the development and progression of bladder cancer and renal cell cancer. Smoking cessation reduces the risks of developing and dying from these common cancers. We quantify these risks using the most up-to-date results published in the literature.

1. Introduction

Tobacco smoke is the commonest human carcinogen. The World Health Organization estimates that in 2013 there were more than one billion smokers worldwide [1] and approximately six million people die each year from tobacco-related illnesses. These deaths include an estimated one million nonsmokers who obtained exposure indirectly from environmental tobacco smoke or secondhand smoking (SHS) [1]. The majority of smoking-related deaths occur because of cardiovascular and pulmonary diseases or malignancies. The risk of tobacco-related illnesses varies with the duration and intensity of smoking [2], the type of tobacco and mode of administration, and an individual's ability to detoxify carcinogens. Tobacco can be consumed in a variety of forms such as smoking cigarettes, cigars, pipes, and shisha (a molasses-tobacco hybrid compound), chewing, and inhalation as snuff, and can be used in isolation or in combination with illicit drugs such as opium and marijuana [3]. Tobacco can be prepared via flue (blonde) or air curing (black). The latter is considered to be more carcinogenic to the urinary tract owing to its higher concentration of nitrosamines, biphenyls, and arylamines [2,4,5]. With regard to carcinogen detoxification, variations in the activity of N-acetyl-transferase 2 (NAT2) and glutathione S-transferase mu μ1 (GSTM1) because of polymorphisms appear to affect cancer risk from smoking [6]. It is also evident that tobacco smoke can induce changes in the DNA damage response machinery, which can additively or synergistically impair the host response to carcinogens [7,8].
Bladder cancer (BC) and renal cell cancer (RCC) are among the commonest smoking-related human malignancies. In 2013 there were an estimated 382 700 new cases of BC and 338 000 of RCC worldwide, with 143 000 and 150 300 resultant deaths, respectively [9,10]. Both tumors are more common in males than females, reflecting the role of tobacco smoking, occupational carcinogen exposure, and lifestyle in their etiology. Tobacco smoke inhalation appears to be the commonest risk factor for BC, accounting for approximately 50% of BC cases [6] and 20–25% of RCC cases [11]. Further risk factors for RCC include obesity and hypertension. For both cancers, risk may be modified by genetic predisposition and interaction with further carcinogens [12], and altering smoking exposure may change the natural history of the disease. For example, smoking cessation may reduce BC recurrence rates [13], although conflicting data exist [14,15]. Regardless of this contradiction, smoking-induced DNA damage (as detected in either blood or urine) reduces to normal levels after cessation [16].
Here we present a systematic review of the literature and meta-analysis of the associations between smoking and both BC and RCC. We analyze both incidence and mortality, and specifically combine risks for SHS and non–smoking-related tobacco exposures. Owing to the causal relationship between active smoking and BC, there has been strong reason to suspect that SHS (also known as environmental tobacco smoke or passive smoking) has a role in carcinogenesis. The strength of this association has been emphasized by evidence that urinary levels of carcinogens are greater in subjects exposed to SHS than those not subjected to this exposure [16].

2. Evidence acquisition

2.1. Systematic review

We searched PubMed in August 2013 for all original articles in English using the string terms "tobacco", "smoking" AND "bladder cancer", and "tobacco", "smoking" AND "kidney cancer". Articles were included in the meta-analysis if they met the following inclusion criteria: (i) case-control, cohort, or nested case-control studies published as original articles in English investigating the relationship between smoking and the risk of BC or RCC in humans; (ii) incidence or disease-specific mortality (DSM) as outcome; and (iii) odds ratio (OR), hazard ratio (HR), or relative risk (RR) estimates with 95% confidence intervals (CIs), or enough information to calculate them, reported. We excluded summary data (reviews) and

reports not focusing on our research question or describing molecular effects in cell lines. In cases of multiple reports from the same series, we used the most recent one. Previous meta-analyses and systematic reviews were only included for discussion purposes when describing potential carcinogenic processes. We report our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [17].

2.2. Data abstraction

From each study included in the meta-analysis, we extracted the first author's last name, publication year, country, study period, gender of study participants, cancer type (BC or RCC), number of cases and controls (for case-control or nested studies) or number of events and cohort size (for cohort studies), smoking status (all, former, or current), tobacco products (cigarettes, cigars, or pipes), SHS exposure, adjustment variables, and RRs or ORs with 95% CIs for each smoking status or tobacco product. If multiple RRs or ORs were presented in the original articles, we extracted the estimates from the maximally adjusted model to reduce the risk of possible unmeasured confounding [18].

2.3. Statistical methods

Because cancer is a relatively rare outcome, we assumed that ORs, risk ratios, and rate ratios were all comparable estimates of the RR. To conduct the meta-analysis, measures of association and the corresponding CIs were translated into log(RR) values and their variances [18].

BC and RCC incidence and DSM risks were computed separately. We used the maximum adjusted risk estimates when reported. We computed pooled RRs for BC and RCC incidence and DSM risks using a random effects model to take into account the heterogeneity between risk estimates [19]. We evaluated potential heterogeneity among studies using the Cochran Q statistic and I^2, that is, the proportion of total variation contributed by between-study variance [20].

To investigate potential sources of heterogeneity, we carried out stratified analyses according to study area (Europe, America, Asia, and Oceania), study design (case-control and cohort studies), and gender. We also tested whether the corresponding stratified pooled RR estimates differed significantly across the strata considered.

Potential publication bias was evaluated by visual inspection of funnel plots, Egger linear regression [21], and the Begg rank correlation test [22].

Stata statistical software (version 12.0, StataCorp LP, College Station, TX, USA) was used for statistical analysis.

3. Evidence synthesis

Our search identified 2683 reports (1237 BC, 225 RCC, 8 both, and 1213 unrelated cancers). All abstracts were read in full by one author (M.G.C.) before selection of 248 papers for extraction. From these full reports, we identified 114 articles (Supplementary Appendix 1) fulfilling our inclusion criteria for the meta-analysis (Supplementary Fig. 1). Outcomes for 51 404 BC cases and 64 602 controls, and for 16 007 RCC cases and 18 876 controls were included in the meta-analysis. Specifically, 109 papers included data on disease incidence or mortality in relation to cigarette smoking, eight papers concentrated on alternative means of tobacco exposure (eg, chewing), and five evaluated SHS (passive smoking). The majority of the reports focused on BC (79%).

3.1. BC incidence

We stratified BC risk according to current, former (no longer smoking at the time of interview), all (data for both current and former smokers, as well as data reported for ever

smokers), and never smoker history (Table 1). There were significant pooled RRs for BC incidence among all smokers of cigarettes (RR 2.57, 95% CI 2.37–2.78; I^2 = 87.7%, p < 0.001), current smokers (RR 3.37, 95% CI 3.01–3.78; I^2 = 82.2%, p < 0.001), and former smokers (RR 1.98, 95% CI 1.76–2.22; I^2 = 78.6%, p < 0.001) when compared to never smokers. Current smokers had the greatest risk (Fig. 1). When stratified by study design, a stronger association between smoking and BC risk was observed in case-control studies than in cohort studies (Table 1). Publication bias for BC among all smokers was assessed using Begg (p = 0.03) and Egger (p = 0.13) tests. Visual inspection of a funnel plot could not rule out publication bias (Supplementary Fig. 2). We further stratified the data by gender and geographic region. Although males (RR 2.55, 95% CI 2.18–2.98; I^2 = 91.6%, p < 0.001) had a slightly higher risk than females (RR 2.19, 95% CI 1.80–2.65; I^2 = 83.3%, p < 0.001), pooled RR estimates did not differ across gender (p = 0.2). The majority of data came from studies based in North America (listed as Americas) and Europe. The highest pooled RR was observed in studies carried out in Europe (RR 2.98, 95% CI 2.67–3.36; I^2 = 86.2%, p < 0.001; Table 3), although we did not see a difference across geographic region (p = 0.08). Among groups that used non-cigarette tobacco, cigar smoking (RR 1.62, 95% CI 1.18–2.22; I^2 = 39.4%, p = 0.2) and pipe smoking (RR 1.49, 95% CI 1.18–1.88; I^2 = 0.0%, p = 0.6) were both associated with significantly higher BC risk (Supplementary Table 2), although pooled RRs estimates were based on just a few studies. We did not observe a significant difference in pooled RR for smoking between non-cigarette tobacco products and cigarettes (p = 0.1).

3.2. BC mortality

BC mortality is less extensively reported in the literature. All smokers (RR 1.79, 95% CI 1.40–2.29; I^2 = 93.3%, p < 0.001), current smokers (RR 1.89, 95% CI 1.29–2.78; I^2 = 90.3%, p < 0.001) and former smokers (RR 1.66, 95% CI 1.10–2.52; I^2 = 95.9%, p < 0.001) had a higher risk of BC mortality compared to never smokers (Table 1). Cigar smoking had a nonsignificant higher mortality risk (data not shown). For current and former smokers, the Begg (p = 1.0 and 0.4) and Egger (p = 0.3 and 0.3) tests for publication bias confirmed that there was no significant publication bias. There were no significant differences by gender (p = 0.9) or geographic region (p = 0.4; Table 3).

3.3. RCC incidence

The risk of developing RCC was significantly higher for all smokers (RR 1.27, 95% CI 1.18–1.35; I^2 = 57.9%, p < 0.001), current smokers (RR 1.29, 95% CI 1.14–1.46; I^2 = 74.4%, p < 0.001), and former smokers (RR 1.14, 95% CI 1.06–1.22; I^2 = 14.5%, p = 0.3; Table 2) compared to nonsmokers. Current smokers had the greatest risk (Fig. 2). Begg and Egger tests for publication bias for all smokers (both p = 0.5), current smokers (p = 0.2 and 0.7, Supplementary Fig. 3), and former smokers (p = 0.9 and 0.3) showed that there was no significant publication bias. A significant difference (p = 0.02) in pooled RRs emerged when we stratified by study geographic region; the greatest pooled RR for RCC was observed for Oceania (RR 1.74, 95% CI 1.14–2.66; I^2 = 70.2%, p = 0.07) and the lowest for Europe (RR 1.02, 95% CI 0.91–1.12; I^2 = 0.0%, p = 0.6). Stratification by gender revealed that males (RR 1.42, 95% CI 1.25–1.62; I^2 =55.0%, p = 0.001) had a slightly higher pooled RR for RCC than females (RR 1.32, 95% CI 1.16–1.51; I^2 = 26.6%, p = 0.14), although the difference was not significant (p = 0.4). There were insufficient data on non-cigarette tobacco use and RCC risk.

3.4. RCC mortality

The risk of death from RCC among tobacco users was elevated for all smokers (RR 1.20, 95% CI 1.02–1.41; I^2 =51.6%, p = 0.044), current smokers (RR 1.32, 95% CI 1.08–1.62; I^2 =25.8%, p = 0.3), and former smokers (RR 1.01, 95% CI 0.85–1.18; I^2 = 14.5%, p = 0.3;

Table 2). Stratification by geographic region revealed that the greatest RR for RCC was in the Americas, but the pooled RR did not differ (p = 0.8), although the numbers are small (Table 3).

3.5. Secondhand smoking

The pooled RR of BC from secondhand smoking was 1.44 (95% CI 1.05–2.0; I^2 = 59.8%, p = 0.021) and of RCC was 1.43 (95% CI 0.89–2.28; I^2 = 55.3%, p = 0.08; data not shown). There were no data on DSM risk for SHS in this data set for either cancer type.

3.6. Discussion

3.6.1. Tobacco products and bladder carcinogenesis

We found that tobacco consumption increases the risk of BC incidence and DSM, and we provide up-to-date and more precise quantitative estimates than previously available [6]. Although certain occupations (such dye workers) may have high individual risk elevations for BC, tobacco smoking appears to be responsible for most BC cases because of its high prevalence [23].

Tobacco is a rich source of polycyclic aromatic hydrocarbons, aromatic amines, and N-nitroso compounds, which cause DNA damage via bulky adduct formation, single- and double-strand DNA breaks, and base modifications [24]. These acquired events complement an individual's genetic predisposition to smoking-related cancer. For example, first-degree relatives of BC patients have a 50–100% higher risk, which increases if the relative was diagnosed at <60 yr of age [25] and in a dose-dependent manner [26].

Tobacco carcinogens are mostly metabolized by xenobiotic enzymes such as N-acetyltransferases (NATs) and glutathione S-transferases. These enzymes have alleles with different activity profiles. For example, individuals with slow NAT2 acetylation exhibit less efficient detoxification of carcinogens, leading to higher accumulation in urothelium. There is general consensus that individuals with slow NAT2 acetylation have a higher BC risk (up to 50%) and that this higher risk is mostly seen in smokers. Approximately 50% of individuals of European, 35% of African, and 15% of Asian descent may have slow acetlyation [23]. Genome-wide association studies have recently focused on interactions between smoking and single nucleotide polymorphisms in BC patients, but a conclusive link has not been shown to date [27].

3.6.2. Tobacco products and renal carcinogenesis

We found that RCC was 1.3-fold more common among smokers, in agreement with previous data [28]. In addition, the RCC DSM risk was 1.3-fold higher among current smokers. The triad of obesity, hypertension, and smoking are accepted as the main contributors to RCC [29–31]. It is thought that obesity confers risk through an increase in lipid peroxidation by-products that can cause DNA adducts [32]. It has also been shown that obese patients have higher circulating levels of insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), which have roles in cell proliferation. Patients with hypertension also have higher levels of lipid peroxidation by-products, and it is thought that hypertension results in renal tubular damage, making the kidney more susceptible to circulating carcinogens [30,32]. It is thought that tobacco smoking adds to this and itself promotes the formation of oxygen free radicals that can cause DNA damage. Tobacco smoking leads to more aggressive RCC phenotypes, and patients who smoke at the time of nephrectomy have a lower survival rate [33,34]. There is no universal consensus on whether this is due to direct effects of tobacco or the characteristics of smokers, who are perhaps less likely to seek health care and may suffer from delayed presentation.

A number of genes increase susceptibility to RCC, including von Hippel-Lindau (VHL) [32]. There are limited data on gene-environment interactions; however, in the last decade a link has been made between obesity and VHL tumor suppressor inactivation through mutations caused by reactive oxygen species [32]. Little is known about smoking and these interactions.

3.6.3. Patient outcomes

Smoking reduces perioperative performance status and impairs wound healing. Consequently, the risk of perioperative complications, disease progression, and tumor recurrence after treatment is higher [35], as is the incidence of second smoking-related cancers after successful treatment [36], among smokers when compared to nonsmokers. Disease-related patterns may differ between the malignancies. For RCC, smoking is associated with higher stage at diagnosis [35]. For BC, post-treatment recurrence risks were elevated in the majority of studies, although the hazard ratio (HR) varied in this review from 1.57 to 3.67 (data not shown) [13,37]. Despite these outcomes, fewer than 50% of patients stop smoking after their cancer diagnosis [38].

3.6.4. Secondhand smoking

One of the main methodologic limitations in measuring the effects of smoking on health outcomes is the difficulty in controlling for and measuring SHS exposure. In the articles included in our meta-analysis, researchers used household exposure, workplace exposure, or any environmental exposure methods to quantify SHS. However, these lack precision and make the strength of conclusions weaker than those for smokers.

3.6.5. Limitations

There are various limitations to our study. In terms of search strategy and data collection, we chose to review only studies we found via the Medline database through PubMed, which may have limited the number of studies included. Furthermore, we only looked at studies written in English. However, a study by Moher et al [39] provides no evidence that language-restricted meta-analyses lead to biased estimates of intervention effectiveness.

In addition, there are concerns about the reliability and validity of smoking status questionnaires and interviews (smokers can under-report consumption or suffer recall bias). Most series were retrospective case-control studies, which may suffer from inaccurate documentation of smoking history. Prospective studies have fewer potential sources of bias, but under-reporting of smoking affects these studies too. Sweeney and Farrow [40] make the interesting point that smokers, who have poorer outcomes, may be under-represented because they deteriorate at an earlier stage compared to nonsmokers, and hence may not be available for studies. It is also accepted that SHS is hard to measure, and contamination is likely to confound risk estimates for nonsmokers [41]. It can be difficult to combine tobacco-smoking studies that may have looked at different tobacco-smoking combinations and used different definitions of smoking status. Hence, we chose not to analyze dose-response data (intensity of smoking) and instead used summary categories. Another potential pitfall of meta-analyses is the failure to appreciate the role of potentially confounding variables. To counter this, we used maximally adjusted risk estimates where provided. While we were not able to stratify for all characteristics (eg, ethnicity), we do report risk estimate differences by gender and geographic region. It would have been interesting to know whether the effect of tobacco smoking on BC incidence and DSM is similar in non–muscle-invasive (NMIBC) and muscle-invasive bladder cancer (MIBC), but studies included in this meta-analysis did not report results according to cancer stage. In 1987, Jensen et al found no difference in the effect of smoking on incidence between NMIBC and MIBC [15].

Finally, during data analysis, Begg and Egger tests provided p values that were not significant for publication bias, even though visual inspection of funnel plots could not completely rule our this possibility.

4. Conclusions

We provide the largest meta-analysis to date on the relationship between tobacco smoking and BC and RCC incidence and mortality. Smoking involves a higher risk of cancer incidence and DSM, consistent with the literature. For BC, the incidence and DSM risk are greatest in current smokers and lowest in former smokers, indicating that cessation confers benefit. In 1988 smoking was responsible for 30–40% of BC and RCC cases [42]. Since then, some authors have suggested there has been an overall modest decrease in incidence and mainly mortality, particularly for BC [43–45]. Obesity is an increasing health problem and is probably partly responsible for the plateau in RCC incidence [42,45]. Despite reductions in occupational exposures and smoking bans, smoking patterns in some countries remain high and the need to promote smoking cessation continues.

Author contributions: Marcus G. Cumberbatch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Catto, Cumberbatch, La Vecchia.
Acquisition of data: Cumberbatch, Rota.
Analysis and interpretation of data: Cumberbatch, Rota.
Drafting of the manuscript: Cumberbatch, Rota, La Vecchia, Catto.
Critical revision of the manuscript for important intellectual content: Rota, La Vecchia.
Statistical analysis: Cumberbatch, Rota.
Obtaining funding: Cumberbatch, Catto.
Administrative, technical, or material support: Cumberbatch.
Supervision: La Vecchia.
Other: None.

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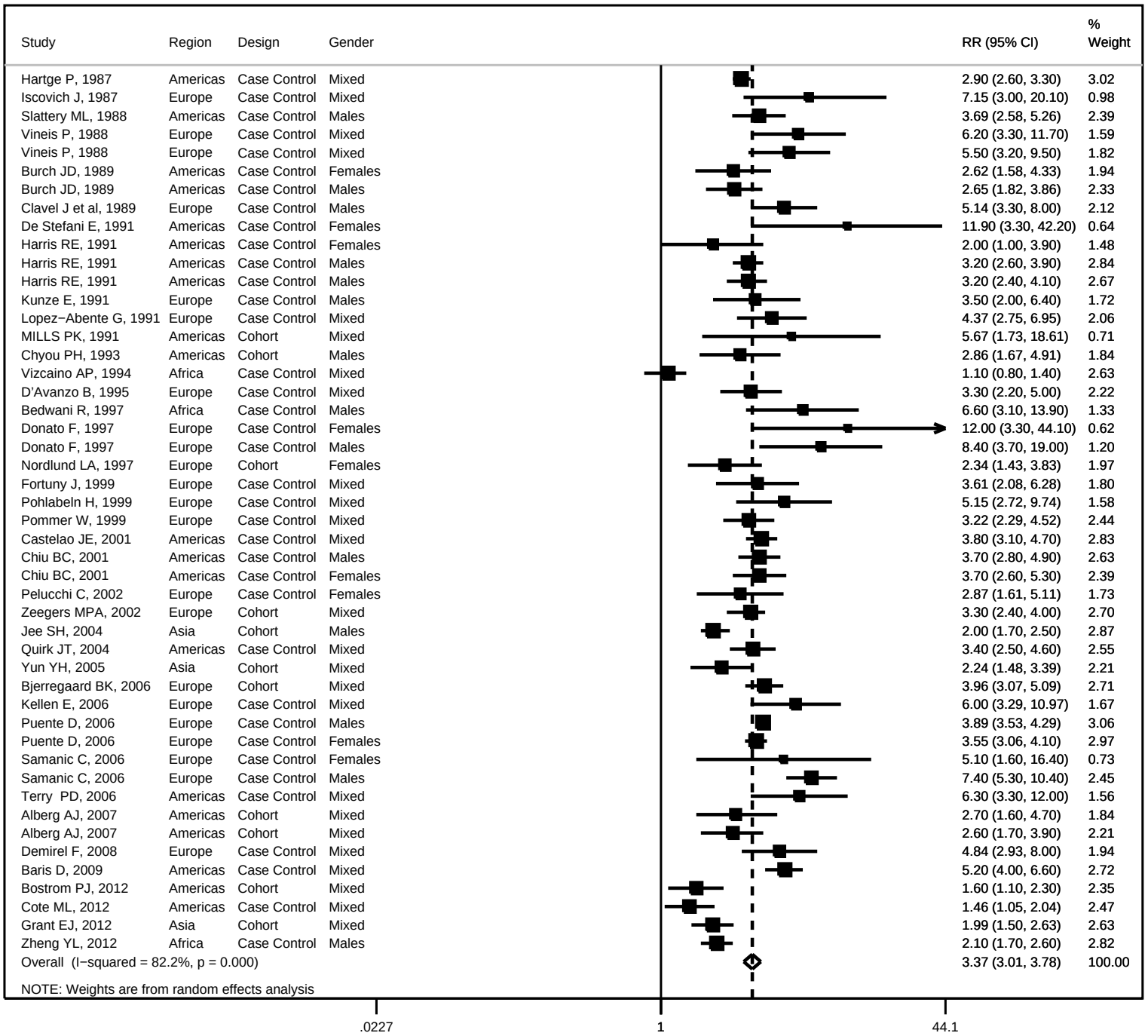
Fig. 1 – Forest plot of study-specific and pooled relative risk (RR) with 95% confidence interval (CI) for the incidence of bladder cancer among current cigarette smokers compared to nonsmokers. The studies are listed in Supplementary Appendix 1.

Fig. 2 – Forest plot of study-specific and pooled relative risk (RR) with 95% confidence interval (CI) for the incidence of renal cell cancer among current cigarette smokers compared to nonsmokers. The studies are listed in Supplementary Appendix 1.

Figure 1


Study
Region
Design
Gender
RR (95% CI)
% Weight
Hartge P, 1987 Americas Case Control Mixed 2.90 (2.60, 3.30) 3.02
Iscovich J, 1987 Europe Case Control Mixed 7.15 (3.00, 20.10) 0.98
Slattery ML, 1988 Americas Case Control Males 3.69 (2.58, 5.26) 2.39
Vineis P, 1988 Europe Case Control Mixed 6.20 (3.30, 11.70) 1.59
Vineis P, 1988 Europe Case Control Mixed 5.50 (3.20, 9.50) 1.82
Burch JD, 1989 Americas Case Control Females 2.62 (1.58, 4.33) 1.94
Burch JD, 1989 Americas Case Control Males 2.65 (1.82, 3.86) 2.33
Clavel J et al, 1989 Europe Case Control Males 5.14 (3.30, 8.00) 2.12
De Stefani E, 1991 Americas Case Control Females 11.90 (3.30, 42.20) 0.64
Harris RE, 1991 Americas Case Control Females 2.00 (1.00, 3.90) 1.48
Harris RE, 1991 Americas Case Control Males 3.20 (2.60, 3.90) 2.84
Harris RE, 1991 Americas Case Control Males 3.20 (2.40, 4.10) 2.67
Kunze E, 1991 Europe Case Control Males 3.50 (2.00, 6.40) 1.72
Lopez−Abente G, 1991 Europe Case Control Mixed 4.37 (2.75, 6.95) 2.06
MILLS PK, 1991 Americas Cohort Mixed 5.67 (1.73, 18.61) 0.71
Chyou PH, 1993 Americas Cohort Males 2.86 (1.67, 4.91) 1.84
Vizcaino AP, 1994 Africa Case Control Mixed 1.10 (0.80, 1.40) 2.63
D'Avanzo B, 1995 Europe Case Control Mixed 3.30 (2.20, 5.00) 2.22
Bedwani R, 1997 Africa Case Control Males 6.60 (3.10, 13.90) 1.33
Donato F, 1997 Europe Case Control Females 12.00 (3.30, 44.10) 0.62
Donato F, 1997 Europe Case Control Males 8.40 (3.70, 19.00) 1.20
Nordlund LA, 1997 Europe Cohort Females 2.34 (1.43, 3.83) 1.97
Fortuny J, 1999 Europe Case Control Mixed 3.61 (2.08, 6.28) 1.80
Pohlabeln H, 1999 Europe Case Control Mixed 5.15 (2.72, 9.74) 1.58
Pommer W, 1999 Europe Case Control Mixed 3.22 (2.29, 4.52) 2.44
Castelao JE, 2001 Americas Case Control Mixed 3.80 (3.10, 4.70) 2.83
Chiu BC, 2001 Americas Case Control Males 3.70 (2.80, 4.90) 2.63
Chiu BC, 2001 Americas Case Control Females 3.70 (2.60, 5.30) 2.39
Pelucchi C, 2002 Europe Case Control Females 2.87 (1.61, 5.11) 1.73
Zeegers MPA, 2002 Europe Cohort Mixed 3.30 (2.40, 4.00) 2.70
Jee SH, 2004 Asia Cohort Males 2.00 (1.70, 2.50) 2.87
Quirk JT, 2004 Americas Case Control Mixed 3.40 (2.50, 4.60) 2.55
Yun YH, 2005 Asia Cohort Mixed 2.24 (1.48, 3.39) 2.21
Bjerregaard BK, 2006 Europe Cohort Mixed 3.96 (3.07, 5.09) 2.71
Kellen E, 2006 Europe Case Control Mixed 6.00 (3.29, 10.97) 1.67
Puente D, 2006 Europe Case Control Males 3.89 (3.53, 4.29) 3.06
Puente D, 2006 Europe Case Control Females 3.55 (3.06, 4.10) 2.97
Samanic C, 2006 Europe Case Control Females 5.10 (1.60, 16.40) 0.73
Samanic C, 2006 Europe Case Control Males 7.40 (5.30, 10.40) 2.45
Terry PD, 2006 Americas Case Control Mixed 6.30 (3.30, 12.00) 1.56
Alberg AJ, 2007 Americas Cohort Mixed 2.70 (1.60, 4.70) 1.84
Alberg AJ, 2007 Americas Cohort Mixed 2.60 (1.70, 3.90) 2.21
Demirel F, 2008 Europe Case Control Mixed 4.84 (2.93, 8.00) 1.94
Baris D, 2009 Americas Case Control Mixed 5.20 (4.00, 6.60) 2.72
Bostrom PJ, 2012 Americas Cohort Mixed 1.60 (1.10, 2.30) 2.35
Cote ML, 2012 Americas Case Control Mixed 1.46 (1.05, 2.04) 2.47
Grant EJ, 2012 Asia Cohort Mixed 1.99 (1.50, 2.63) 2.63
Zheng YL, 2012 Africa Case Control Males 2.10 (1.70, 2.60) 2.82
Overall (I−squared = 82.2%, p = 0.000) 3.37 (3.01, 3.78) 100.00
NOTE: Weights are from random effects analysis
.0227
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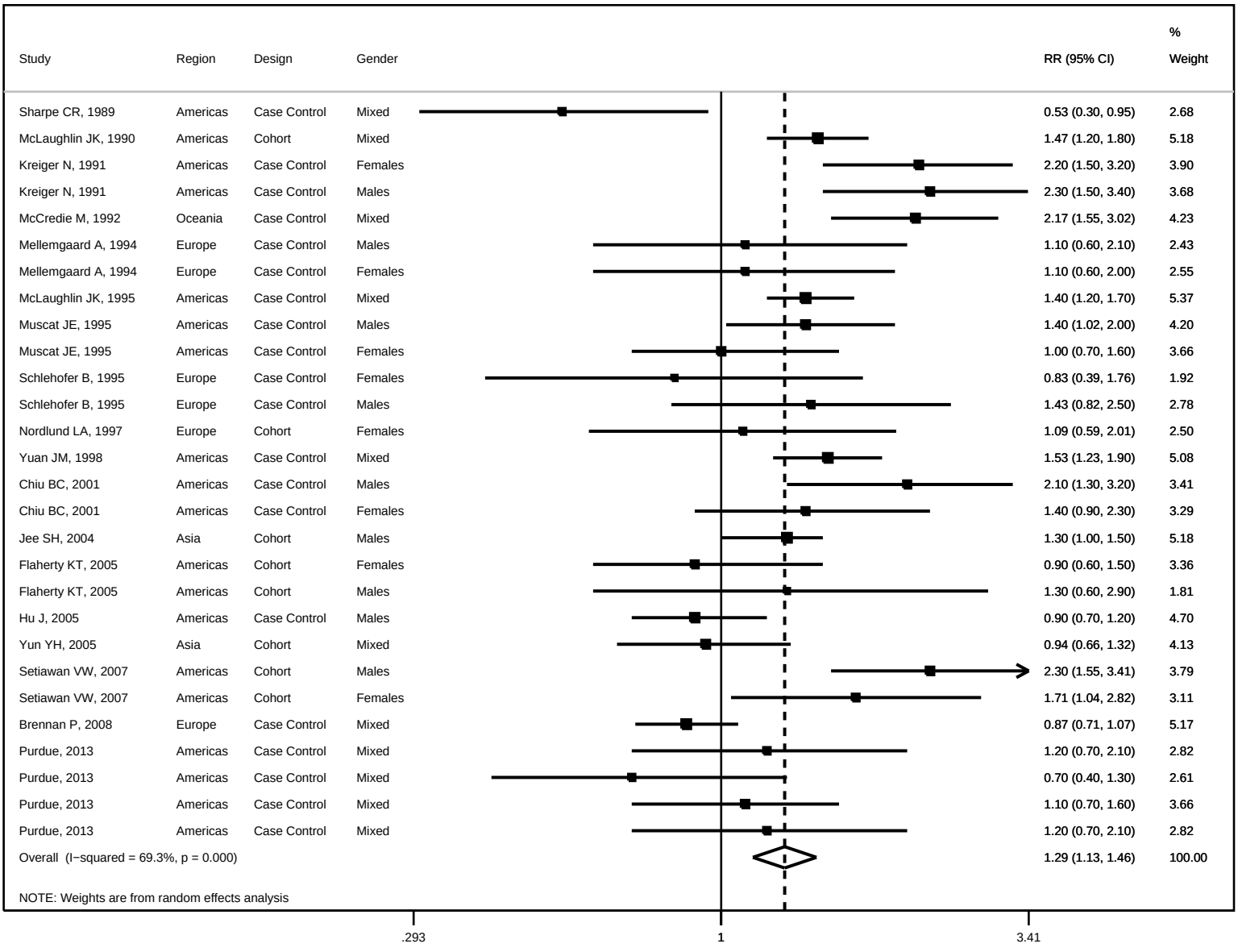
44.1

Figure 2


Study
Region
Design
Gender
RR (95% CI)
% Weight
Sharpe CR, 1989 Americas Case Control Mixed 0.53 (0.30, 0.95) 2.68
McLaughlin JK, 1990 Americas Cohort Mixed 1.47 (1.20, 1.80) 5.18
Kreiger N, 1991 Americas Case Control Females 2.20 (1.50, 3.20) 3.90
Kreiger N, 1991 Americas Case Control Males 2.30 (1.50, 3.40) 3.68
McCredie M, 1992 Oceania Case Control Mixed 2.17 (1.55, 3.02) 4.23
Mellemgaard A, 1994 Europe Case Control Males 1.10 (0.60, 2.10) 2.43
Mellemgaard A, 1994 Europe Case Control Females 1.10 (0.60, 2.00) 2.55
McLaughlin JK, 1995 Americas Case Control Mixed 1.40 (1.20, 1.70) 5.37
Muscat JE, 1995 Americas Case Control Males 1.40 (1.02, 2.00) 4.20
Muscat JE, 1995 Americas Case Control Females 1.00 (0.70, 1.60) 3.66
Schlehofer B, 1995 Europe Case Control Females 0.83 (0.39, 1.76) 1.92
Schlehofer B, 1995 Europe Case Control Males 1.43 (0.82, 2.50) 2.78
Nordlund LA, 1997 Europe Cohort Females 1.09 (0.59, 2.01) 2.50
Yuan JM, 1998 Americas Case Control Mixed 1.53 (1.23, 1.90) 5.08
Chiu BC, 2001 Americas Case Control Males 2.10 (1.30, 3.20) 3.41
Chiu BC, 2001 Americas Case Control Females 1.40 (0.90, 2.30) 3.29
Jee SH, 2004 Asia Cohort Males 1.30 (1.00, 1.50) 5.18
Flaherty KT, 2005 Americas Cohort Females 0.90 (0.60, 1.50) 3.36
Flaherty KT, 2005 Americas Cohort Males 1.30 (0.60, 2.90) 1.81
Hu J, 2005 Americas Case Control Males 0.90 (0.70, 1.20) 4.70
Yun YH, 2005 Asia Cohort Mixed 0.94 (0.66, 1.32) 4.13
Setiawan VW, 2007 Americas Cohort Males 2.30 (1.55, 3.41) 3.79
Setiawan VW, 2007 Americas Cohort Females 1.71 (1.04, 2.82) 3.11
Brennan P, 2008 Europe Case Control Mixed 0.87 (0.71, 1.07) 5.17
Purdue, 2013 Americas Case Control Mixed 1.20 (0.70, 2.10) 2.82
Purdue, 2013 Americas Case Control Mixed 0.70 (0.40, 1.30) 2.61
Purdue, 2013 Americas Case Control Mixed 1.10 (0.70, 1.60) 3.66
Purdue, 2013 Americas Case Control Mixed 1.20 (0.70, 2.10) 2.82
Overall (I−squared = 69.3%, p = 0.000) 1.29 (1.13, 1.46) 100.00
NOTE: Weights are from random effects analysis
.293
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3.41

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Instructions to typesetter

Figure 1
Change I-squared to I^2
Use italic *p* for $p = 0.000$
Change Case Control to Case-control

Figure 2
Change I-squared to I^2
Use italic *p* for $p = 0.000$
Change Case Control to Case-control

Table

Table 1 – Pooled relative risk (PRR) and 95% confidence interval (CI) for bladder cancer incidence and mortality by selected cigarette smoking status compared to nonsmokers

	Incidence			Mortality		
	n [a]	PRR (95% CI)	I^2, % (p value [b])	n [a]	PRR (95% CI)	I^2, % (p value [b])
All smokers						
Case-control studies	119	2.73 (2.50–2.99)	89.4 (<0.001)	–	–	–
Cohort studies	33	2.06 (1.80–2.35)	68.3 (<0.001)	19	1.79 (1.40–2.29)	<0.001
Overall	152	2.57 (2.37–2.78)	87.7 (<0.001)	19	1.79 (1.40–2.29)	93.3 (<0.001)
Ever smokers						
Case-control studies	48	2.62 (2.28–3.03)	89.1 (<0.001)	0	–	–
Cohort studies	7	1.52 (1.25–1.83)	0.0 (0.7)	2	1.84 (0.74–4.59)	94.3 (<0.001)
Overall	55	2.46 (2.16–2.81)	87.9 (<0.001)	2	1.84 (0.74–4.59)	93.1 (<0.001)
Current smokers						
Case-control studies	37	3.68 (3.24–4.18)	82.0 (<0.001)	0	–	–
Cohort studies	11	2.53 (2.07–3.09)	69.8 (<0.001)	9	1.89 (1.29–2.78)	90.3 (<0.001)
Overall	48	3.37 (3.01–3.78)	82.2 (<0.001)	9	1.89 (1.29–2.78)	90.3 (<0.001)
Former smokers						
Case-control studies	34	2.00 (1.73–2.31)	82.2 (<0.001)	0	–	–
Cohort studies	15	1.94 (1.59–2.36)	63.3 (<0.001)	8	1.66 (1.10–2.52)	95.9 (<0.001)
Overall	49	1.98 (1.76–2.22)	78.6 (<0.001)	8	1.66 (1.10–2.52)	95.9 (<0.001)

[a] Number of comparisons. Some studies include separate estimates for males and females and for smoking category.
[b] p value for heterogeneity.

Table 2 – Pooled relative risk (PRR) and 95% confidence interval (CI) for renal cell cancer incidence and mortality by selected cigarette smoking status compared to nonsmokers

	Incidence			Mortality		
	n [a]	PRR (95% CI)	I^2, % (p value [b])	n [a]	PRR (95% CI)	I^2, % (p value [b])
All smokers						
Case-control studies	52	1.25 (1.15–1.36)	64.0 (<0.001)	–	–	–
Cohort studies	18	1.31 (1.19–1.44)	18.1 (0.2)	8	1.20 (1.02–1.41)	51.6 (<0.044)
Overall	70	1.27 (1.18–1.35)	57.9 (<0.001)	8	1.20 (1.02–1.41)	51.6 (<0.044)
Ever smokers						
Case-control studies	14	1.45 (1.27–1.66)	45.4 (0.034)	0	–	–
Cohort studies	0	–	–	1	–	–
Overall	14	1.45 (1.27–1.66)	45.4 (0.034)	1	1.30 (0.92–1.84)	–
Current smokers						
Case-control studies	20	1.27 (1.08–1.49)	78.5 (<0.001)	0	–	–
Cohort studies	8	1.33 (1.01–1.63)	57.2 (<0.023)	4	1.32 (1.08–1.62)	25.8 (0.3)
Overall	28	1.29 (1.14–1.46)	74.4 (<0.001)	4	1.32 (1.08–1.62)	25.8 (0.3)
Former smokers						
Case-control studies	18	1.09 (0.997–1.19)	26.5 (0.2)	0	–	–
Cohort studies	10	1.26 (1.12–1.43)	0.0 (0.9)	3	1.01 (0.85–1.18)	14.5 (0.3)
Overall	28	1.14 (1.06–1.22)	14.5 (0.3)	3	1.01 (0.85–1.18)	14.5 (0.3)

[a] Number of comparisons. Some studies include separate estimates for males and females and for smoking category.
[b] p value for heterogeneity.

Table 3 – Pooled relative risk (PRR) and 95% confidence interval (CI) for bladder and renal cell cancer incidence and mortality for ever cigarette smokers compared to nonsmokers stratified by gender and geographic region

	Incidence			Mortality		
	n [a]	PRR (95% CI)	I^2, % (p value [b])	n [a]	PRR (95% CI)	I^2, % (p value [b])
Bladder cancer						
Gender [c]						
Male	43	2.55 (2.18–2.98)	91.6 (<0.001)	7	2.45 (1.61–3.14)	90.7 (<0.001)
Female	33	2.19 (1.80–2.65)	83.3 (<0.001)	3	2.49 (1.45–4.27)	87.3 (<0.001)
Mixed	76	2.74 (2.47–3.04)	85.9 (<0.001)	8	1.35 (1.00–1.80)	86.4 (<0.001)
Study area						
Europe	66	2.98 (2.67–3.36)	86.2 (<0.001)	6	2.26 (1.87–2.72)	37.6 (0.2)
Asia	16	2.26 (1.79–2.86)	83.3 (<0.001)	5	1.56 (1.24–1.97)	0.0 (0.8)
Americas	62	2.36 (2.10–2.65)	88.6 (<0.001)	8	1.77 (1.10–2.82)	97.2 (<0.001)
Africa	8	2.01 (1.25–3.21)	88.5 (<0.001)	0	–	–
Renal cell cancer						
Gender [c]						
Male	21	1.42 (1.25–1.62)	55.0 (0.001)	3	1.12 (0.85–1.47)	0.0 (0.6)
Female	19	1.32 (1.16–1.51)	26.6 (<0.14)	–	–	–
Mixed	30	1.16 (1.06–1.27)	65.0 (<0.001)	4	1.23 (0.99–1.53)	70.3 (0.009)
Study area						
Europe	16	1.02 (0.91–1.12)	0.0 (0.6)	1	1.30 (0.92–1.84)	–
Asia	5	1.19 (1.01–1.41)	27.9 (0.2)	3	1.12 (0.85–1.47)	0.0 (0.6)
Americas	46	1.30 (1.20–1.40)	61.9 (<0.001)	4	1.22 (0.95–1.58)	76.8 (0.005)
Oceania	2	1.74 (1.14–2.66)	70.2 (0.07)	0	–	–

[a] Number of comparisons. Some studies include separate estimates for males and females and/or smoking category.

[b] p value for heterogeneity.

[c] The sum does not add up to the total number of studies in the meta–analysis since only studies reporting estimates separately for men and women were selected.

Supplementary figure 1

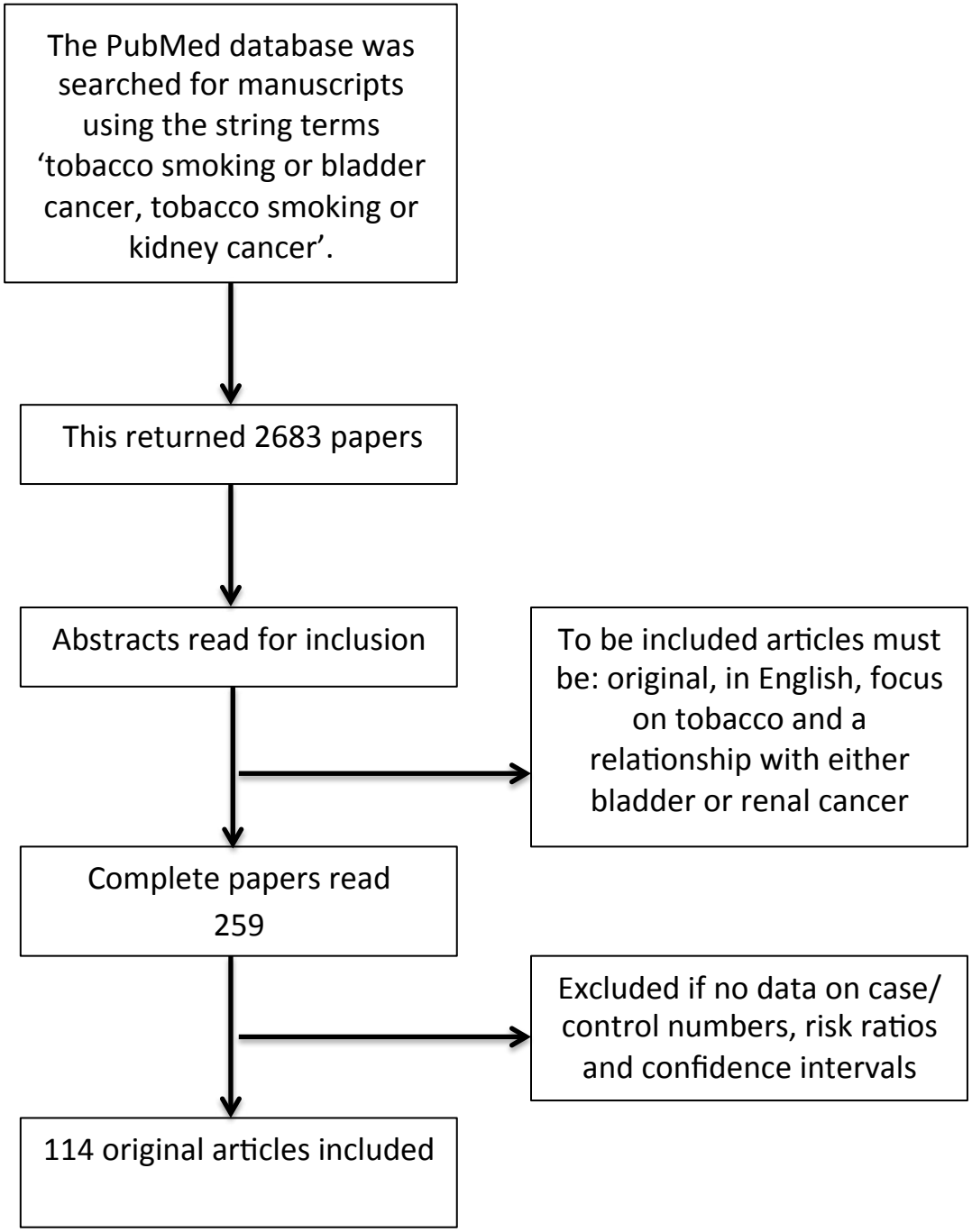
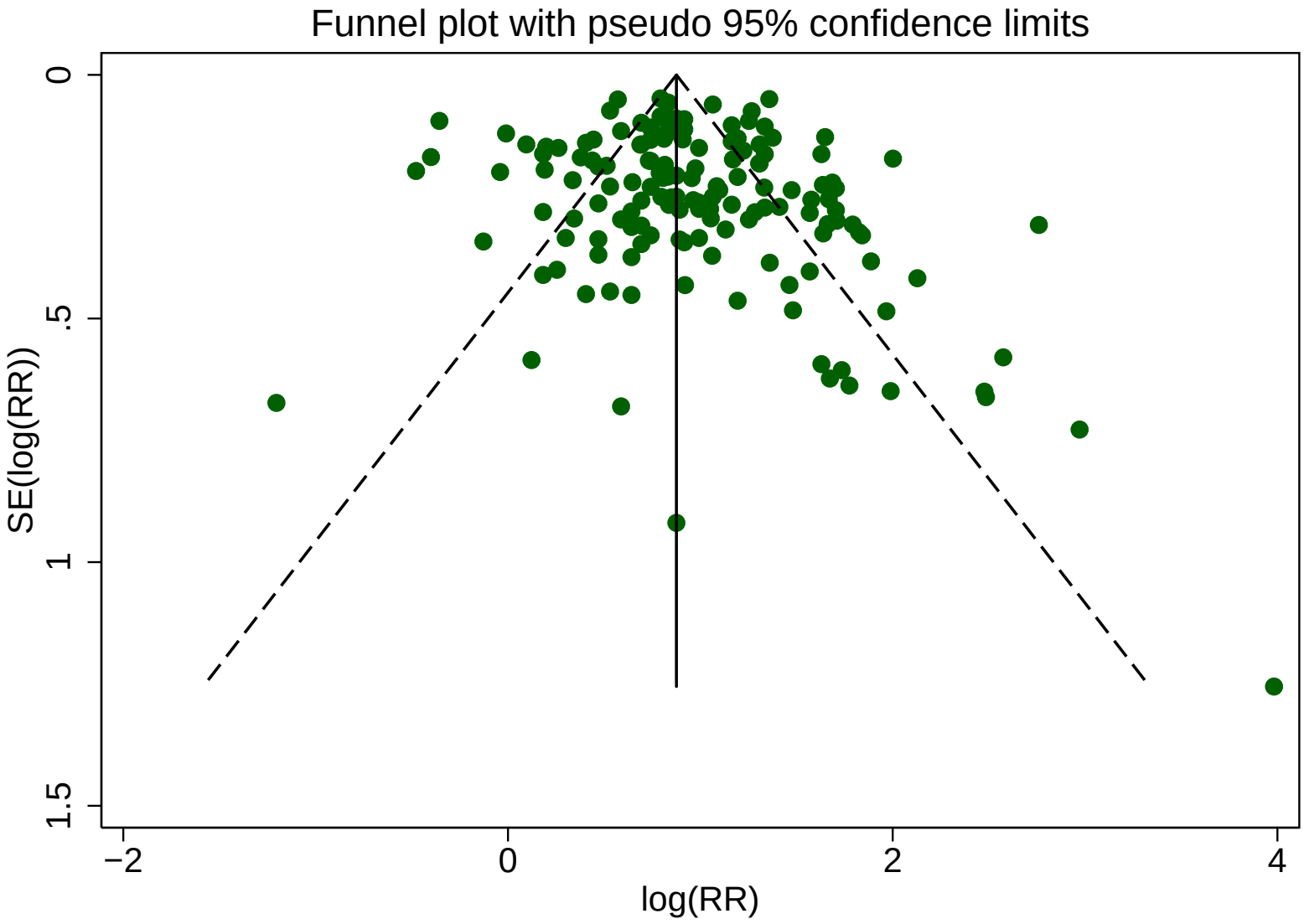
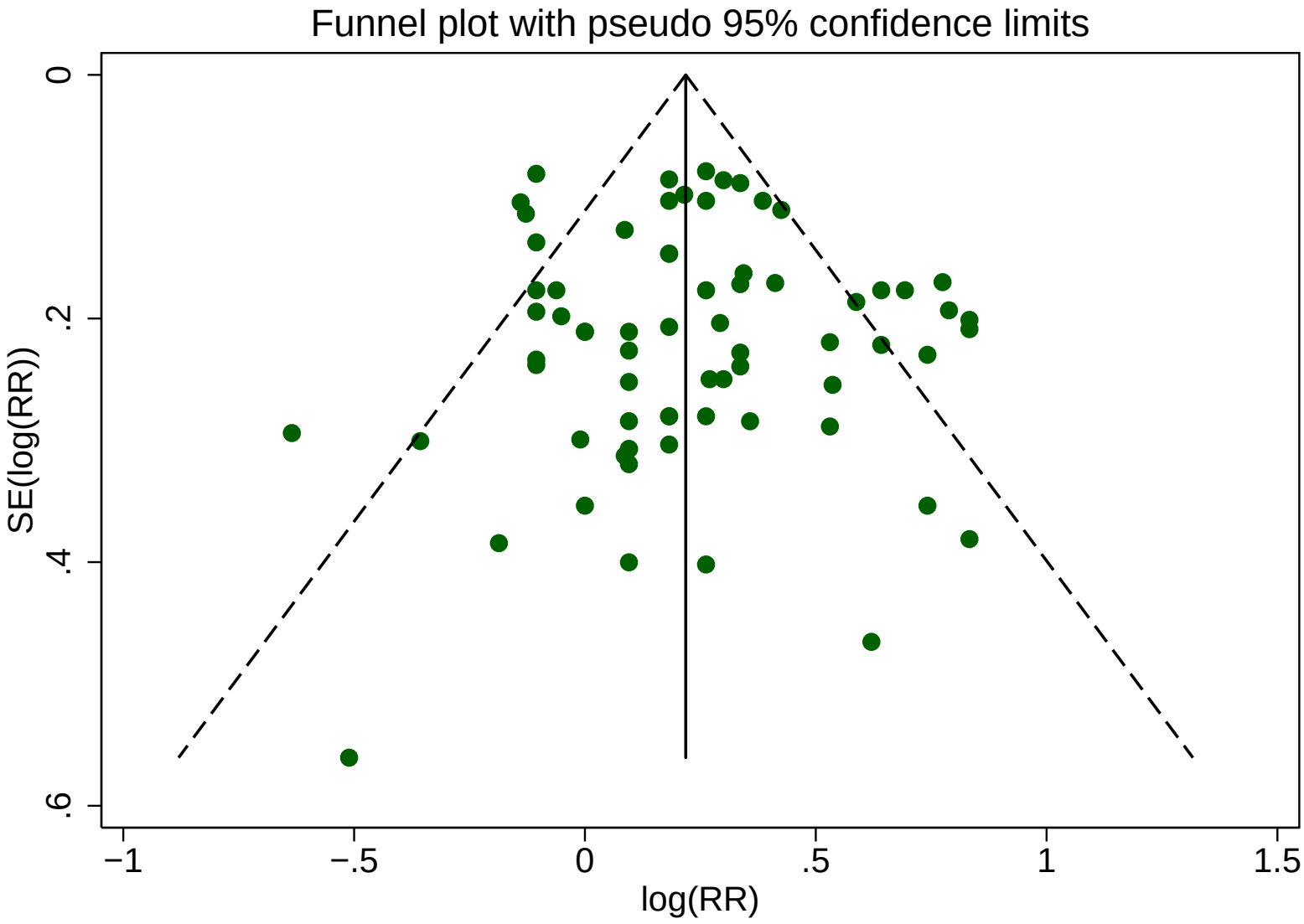


Figure 1.

Supplementary figure 2



Supplementary figure 3



Supplementary Figure 1 Flowchart of selection of studies for inclusion in the meta-analysis.

Supplementary Figure 2 Funnel plot for incidence of Bladder Cancer in relation to all cigarette smoking with respect to nonsmoking.

Supplementary Figure 3 Funnel plot for incidence of Renal Cell Cancer in relation to all cigarette smoking with respect to nonsmoking.

Appendix 1. List of studies included in the meta-analysis.

1. Miller CT, Neutel CI, Nair RC, Marrett LD, Last JM, Collins WE. Relative importance of risk factors in bladder carcinogenesis. Journal of chronic diseases. 1978;31:51-6.

2. Najem GR, Louria DB, Seebode JJ, Thind IS, Prusakowski JM, Ambrose RB, et al. Life time occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. International journal of epidemiology. 1982;11:212-7.

3. Cartwright RA, Adib R, Appleyard I, Glashan RW, Gray B, Hamilton-Stewart PA, et al. Cigarette smoking and bladder cancer: an epidemiological inquiry in West Yorkshire. Journal of epidemiology and community health. 1983;37:256-63.

4. Mommsen S, Aagaard J, Sell A. A case-control study of female bladder cancer. European journal of cancer & clinical oncology. 1983;19:725-9.

5. McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni JF, Jr. A population--based case--control study of renal cell carcinoma. Journal of the National Cancer Institute. 1984;72:275-84.

6. Hartge P, Hoover R, Kantor A. Bladder cancer risk and pipes, cigars, and smokeless tobacco. Cancer. 1985;55:901-6.

7. Rebelakos 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. Journal of the National Cancer Institute. 1985;75:455-61.

8. Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H. Life-style and occupational risk factors in cancer of the lower urinary tract. American journal of epidemiology. 1986;124:578-89.

9. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. American journal of epidemiology. 1986;124:926-41.

10. Piper JM, Matanoski GM, Tonascia J. Bladder cancer in young women. American journal of epidemiology. 1986;123:1033-42.

11. Yu MC, Mack TM, Hanisch R, Cicioni C, Henderson BE. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. Journal of the National Cancer Institute. 1986;77:351-6.

12. 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. Journal of the National Cancer Institute. 1987;78:1119-25.

13. Iscovich J, Castelletto R, Esteve J, Munoz N, Colanzi R, Coronel A, et al. Tobacco smoking, occupational exposure and bladder cancer in Argentina. International journal of cancer Journal international du cancer. 1987;40:734-40.

14. Jensen OM, Wahrendorf J, Blettner M, Knudsen JB, Sorensen BL. The Copenhagen case-control study of bladder cancer: role of smoking in invasive and non-invasive bladder tumours. Journal of epidemiology and community health. 1987;41:30-6.

15. Schifflers E, Jamart J, Renard V. Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium. International journal of cancer Journal international du cancer. 1987;39:287-92.

16. Augustine A, Hebert JR, Kabat GC, Wynder EL. Bladder cancer in relation to cigarette smoking. Cancer research. 1988;48:4405-8.

17. 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.

18. Steineck G, Norell SE, Feychting M. Diet, tobacco and urothelial cancer. A 14-year follow-up of 16,477 subjects. Acta oncologica. 1988;27:323-7.

19. 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 research. 1988;48:3849-52.

20. 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. International journal of cancer Journal international du cancer. 1989;44:622-8.

21. Clavel J, Cordier S, Boccon-Gibod L, Hemon D. Tobacco and bladder cancer in males: increased risk for inhalers and smokers of black tobacco. International journal of cancer Journal international du cancer. 1989;44:605-10.

22. Nomura A, Kolonel LN, Yoshizawa CN. Smoking, alcohol, occupation, and hair dye use in cancer of the lower urinary tract. American journal of epidemiology. 1989;130:1159-63.

23. Sharpe CR, Rochon JE, Adam JM, Suissa S. Case-control study of hydrocarbon exposures in patients with renal cell carcinoma. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 1989;140:1309-18.

24. Akiba S, Hirayama T. Cigarette smoking and cancer mortality risk in Japanese men and women--results from reanalysis of the six-prefecture cohort study data. Environmental health perspectives. 1990;87:19-26.

25. 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.

26. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Smoking and renal cell carcinoma. Cancer research. 1990;50:5231-3.

27. McLaughlin JK, Hrubec Z, Heineman EF, Blot WJ, Fraumeni JF, Jr. Renal cancer and cigarette smoking in a 26-year followup of U.S. veterans. Public health reports. 1990;105:535-7. renal cancer (RCC not specified but assumed)

28. Talamini R, Baron AE, Barra S, Bidoli E, La Vecchia C, Negri E, et al. A case-control study of risk factor for renal cell cancer in northern Italy. Cancer causes & control : CCC. 1990;1:125-31.

29. Burns PB, Swanson GM. Risk of urinary bladder cancer among blacks and whites: the role of cigarette use and occupation. Cancer causes & control : CCC. 1991;2:371-9.

30. 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.

31. 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. American journal of epidemiology. 1991;134:830-9.

32. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. American journal of epidemiology. 1991;133:230-9.

33. Brooks DR, Geller AC, Chang J, Miller DR. Occupation, smoking, and the risk of high-grade invasive bladder cancer in Missouri. American journal of industrial medicine. 1992;21:699-713.

34. 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.

35. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales--I. Cigarette smoking. European journal of cancer. 1992;28A:2050-4.

36. McLaughlin JK, Gao YT, Gao RN, Zheng W, Ji BT, Blot WJ, et al. Risk factors for renal-cell cancer in Shanghai, China. International journal of cancer Journal international du cancer. 1992;52:562-5.

37. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. Annals of epidemiology. 1993;3:211-6.

38. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: results of a population-based case-control study. Cancer causes & control : CCC. 1993;4:101-10.

39. Wakai K, Ohno Y, Obata K, Aoki K. Prognostic significance of selected lifestyle factors in urinary bladder cancer. Japanese journal of cancer research : Gann. 1993;84:1223-9.

40. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. Cancer causes & control : CCC. 1994;5:105-13.

41. 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. European journal of epidemiology. 1994;10:599-604.

42. Siemiatycki J, Dewar R, Krewski D, Desy M, Richardson L, Franco E. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? Epidemiology. 1994;5:57-65.

43. Vizcaino AP, Parkin DM, Boffetta P, Skinner ME. Bladder cancer: epidemiology and risk factors in Bulawayo, Zimbabwe. Cancer causes & control : CCC. 1994;5:517-22.

44. Zhang ZF, Sarkis AS, Cordon-Cardo C, Dalbagni G, Melamed J, Aprikian A, et al. Tobacco smoking, occupation, and p53 nuclear overexpression in early stage bladder cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 1994;3:19-24.

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Table

Supplementary table 1a All study data for Bladder Cancer Incidence

Author	Year	Years of follow up	Journal	Region	Study Design	Risk group	Cases	Controls	Gender	Risk effect	Lower CI	Upper CI
Ahmad MR, 2010	2010	2009	J Ayub Med Coll Abbottabad.	Asia	Case Control	Ever smoker	50	100	Mixed	19.5	4.7	81.3
Ahmad MR, 2012	2012	1987-2005	JPMA	Asia	Case Control	Ever smoker	50	99	Mixed	13.1	4.2	40.9
Akiba S et al, 1990	1990	1966-1981	Environmental Health Perspectives	Asia	Cohort	Ever smoker	120	0	Males	1.7	1.1	2.7
Akiba S et al, 1990	1990	1966-1981	Environmental Health Perspectives	Asia	Cohort	Ever smoker	13	0	Females	1.9	1.0	3.4
Alberg AJ, 2007	2007	1963 and 1975	Am J Epi	Americas	Cohort	Ex smoker	11	0	Mixed	1.2	0.50	2.5
Alberg AJ, 2007	2007	1963 and 1975	Am J Epi	Americas	Cohort	Ex smoker	57	0	Mixed	2.3	1.5	3.4
Alberg AJ, 2007	2007	1963 and 1975	Am J Epi	Americas	Cohort	Current smoker	67	0	Mixed	2.6	1.7	3.9
Alberg AJ, 2007	2007	1963 and 1975	Am J Epi	Americas	Cohort	Current smoker	48	0	Mixed	2.7	1.6	4.7
Augustine A, 1988	1988	1969-1984	Cancer res	Americas	Case Control	Ever smoker	65	205	Females	0.62	0.42	0.91
Augustine A, 1988	1988	1969-1984	Cancer res	Americas	Case Control	Ever smoker	390	1121	Males	0.70	0.58	0.84
Baena AV, 2006	2006	1989-1995	Eur J Cancer Prev	Europe	Case Control	Ever smoker	73	63	Males	53.7	4.6	628.0
Baris D, 2009	2009	2001-2004	J Natl Cancer Inst	Americas	Case Control	Ex smoker	602	698	Mixed	2.3	1.9	2.8
Baris D, 2009	2009	2001-2004	J Natl Cancer Inst	Americas	Case Control	Current smoker	374	204	Mixed	5.2	4.0	6.6
Bedwani R,	1997	1994-1996	Int J cancer	Africa	Case	Ex smoker	28	22	Males	4.4	1.7	11.3

1997					Control							
Bedwani R, 1997	1997	1994-1996	Int J cancer	Africa	Case Control	Current smoker	109	79	Males	6.6	3.1	13.9
Bjerregaard BK, 2006	2006	1991-2004	Int J Cancer	Europe	Cohort	Ex smoker	184	0	Mixed	2.3	1.7	2.9
Bjerregaard BK, 2006	2006	1991-2004	Int J Cancer	Europe	Cohort	Current smoker	234	0	Mixed	4.0	3.1	5.1
Bjerregaard BK, 2006	2006	1992-2004	Cancer causes Control	Europe	Cohort	Ex smoker	62	0	Mixed	5.5	3.1	9.9
Bostrom PJ, 2012	2012	1986-2008	BJU Int	Americas	Cohort	Current smoker	174	0	Mixed	1.6	1.1	2.3
Brennan P, 2001	2001	1976-1996	CCC	Europe	Case Control	Ex smoker	101	314	Females	0.67	0.48	0.93
Brooks DR, 1992	1992	1984-88	Am J Ind Med	Americas	Cohort	Ever smoker	372	0	Mixed	1.5	1.1	1.9
Burch JD, 1989	1989	1979-1982	Int J Cancer	Americas	Case Control	Ex smoker	36	40	Females	1.2	0.69	2.1
Burch JD, 1989	1989	1979-1982	Int J Cancer	Americas	Case Control	Ex smoker	287	305	Males	1.7	1.2	2.4
Burch JD, 1989	1989	1979-1982	Int J Cancer	Americas	Case Control	Ever smoker	118	85	Females	1.9	1.2	2.9
Burch JD, 1989	1989	1979-1982	Int J Cancer	Americas	Case Control	Ever smoker	566	490	Males	2.1	1.5	2.9
Burch JD, 1989	1989	1979-1982	Int J Cancer	Americas	Case Control	Current smoker	82	45	Females	2.6	1.6	4.3
Burch JD, 1989	1989	1979-1982	Int J Cancer	Americas	Case Control	Current smoker	279	185	Males	2.7	1.8	3.9
Burns PB, 1991	1991	1980	CCC	Americas	Case Control	Ever smoker	1176	1112	Males	2.3	1.9	2.7
Burns PB, 1991	1991	1980	CCC	Americas	Case Control	Ever smoker	313	656	Females	2.4	1.9	2.7
Burns PB, 1991	1991	1980	CCC	Americas	Case Control	Ever smoker	132	237	Males	3.0	1.9	4.8

Burns PB, 1991	1991	1980	CCC	Americas	Case Control	Ever smoker	56	146	Females	3.8	2.2	6.4
Cao W, 2005	2005	1994-1997	Cancer	Americas	Case Control	Ever smoker	191	92	Mixed	3.1	1.7	5.9
Cartwright RA, 1983	1983	1978-1981	J Epidemiol Community Health	Europe	Case Control	Ever smoker	150	211	Females	1.2	0.92	1.6
Cartwright RA, 1983	1983	1978-1981	J Epidemiol Community Health	Europe	Case Control	Ever smoker	840	1245	Males	1.6	1.2	2.0
Castelao JE, 2001	2001	1987-1996	J Natl Cancer Inst	Americas	Case Control	Ever smoker	1240	972	Mixed	2.5	2.1	3.0
Castelao JE, 2001	2001	1987-1996	J Natl Cancer Inst	Americas	Case Control	Current smoker	693	362	Mixed	3.8	3.1	4.7
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Ever smoker	950	1068	Males	2.5	2.0	3.1
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Ever smoker	168	259	Females	2.7	2.0	3.6
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Current smoker	139	435	Males	3.7	2.8	4.9
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Current smoker	149	574	Females	3.7	2.6	5.3
Chyou PH, 1993	1993	1965-1968	Ann Epidemiol	Americas	Cohort	Ex smoker	19	2070	Males	1.4	0.70	2.6
Chyou PH, 1993	1993	1965-1968	Ann Epidemiol	Americas	Cohort	Current smoker	60	3435	Males	2.9	1.7	4.9
Claude J, 1986	1986	1977-1982	Am J Epidemiol	Europe	Case Control	Ever smoker	287	238	Males	2.3	1.6	3.3
Claude J, 1986	1986	1977-1982	Am J Epidemiol	Europe	Case Control	Ever smoker	32	15	Females	2.9	1.4	6.0
Clavel J et al, 1989	1989	1984-1987	Int J Cancer	Europe	Case Control	Ex smoker	179	182	Males	3.0	1.9	4.6
Clavel J et al, 1989	1989	1984-1987	Int J Cancer	Europe	Case Control	Current smoker	259	171	Males	5.1	3.3	8.0
Cote ML, 2012	2012	2004-2008	Cancer	Americas	Case	Ex smoker	304	276	Mixed	0.99	0.78	1.3

			Epidemiol Biomarkers prev		Control							
Cote ML, 2012	2012	2004-2008	Cancer Epidemiol Biomarkers prev	Americas	Case Control	Current smoker	209	124	Mixed	1.5	1.1	2.0
D'Avanzo B, 1995	1995	1985-1993	Ann Epidemiol	Europe	Case Control	Ex smoker	176	179	Mixed	2.2	1.5	3.3
D'Avanzo B, 1995	1995	1985-1993	Ann Epidemiol	Europe	Case Control	Current smoker	165	118	Mixed	3.3	2.2	5.0
De Stefani E, 1991	1991	1987-1989	Cancer	Americas	Case Control	Ex smoker	36	79	Males	5.9	1.7	20.7
De Stefani E, 1991	1991	1987-1989	Cancer	Americas	Case Control	Current smoker	52	64	Females	11.9	3.3	42.2
Demirel F, 2008	2008	2001-2006	Int Urol Nephrol	Europe	Case Control	Ex smoker	56	76	Mixed	4.1	2.4	7.0
Demirel F, 2008	2008	2001-2006	Int Urol Nephrol	Europe	Case Control	Current smoker	80	92	Mixed	4.8	2.9	8.0
Donato F, 1997	1997	1990-1992	Eur J Epidemiol	Europe	Case Control	Ex smoker	3	12	Females	2.4	0.40	14.7
Donato F, 1997	1997	1990-1992	Eur J Epidemiol	Europe	Case Control	Ex smoker	61	161	Males	4.8	2.2	10.7
Donato F, 1997	1997	1990-1992	Eur J Epidemiol	Europe	Case Control	Current smoker	66	114	Males	8.4	3.7	19.0
Donato F, 1997	1997	1990-1992	Eur J Epidemiol	Europe	Case Control	Current smoker	15	36	Females	12.0	3.3	44.1
Engeland A, 1996	1996	1964-1965	CCC	Europe	Cohort	Ex smoker	6	0	Females	1.5	0.60	3.5
Engeland A, 1996	1996	1964-1965	CCC	Europe	Cohort	Ex smoker	62	0	Males	2.1	1.3	3.2
Fortuny J, 1999	1999	1975-1995	Int J Cancer	Europe	Case Control	Ex smoker	41	267	Mixed	1.4	0.79	2.5
Fortuny J, 1999	1999	1975-1995	Int J Cancer	Europe	Case Control	Current smoker	65	185	Mixed	3.6	2.1	6.3

Grant EJ, 2012	2012	1963-1991	Radiat Res	Asia	Cohort	Ex smoker	45	0	Mixed	1.2	0.83	1.8
Grant EJ, 2012	2012	1963-1991	Radiat Res	Asia	Cohort	Current smoker	213	0	Mixed	2.0	1.5	2.6
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Ex smoker	67	241	Males	1.3	1.0	1.8
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Ex smoker	20	59	Females	1.6	0.80	3.4
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Current smoker	48	136	Females	2.0	1.0	3.9
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Ex smoker	358	1054	Males	2.1	1.7	2.6
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Current smoker	591	1174	Males	3.2	2.6	3.9
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Current smoker	184	293	Males	3.2	2.4	4.1
Harris RE, 1991	1991	1969-1991	Cancer	Americas	Case Control	Ever smoker	26	35	Females	3.9	1.5	6.8
Hartge P, 1987	1987	1977-1978	J Natl Cancer Inst	Americas	Case Control	Ex smoker	2324	3581	Mixed	1.7	1.5	2.0
Hartge P, 1987	1987	1977-1978	J Natl Cancer Inst	Americas	Case Control	Ever smoker	2324	3581	Mixed	2.3	2.0	2.5
Hartge P, 1987	1987	1977-1978	J Natl Cancer Inst	Americas	Case Control	Current smoker	2324	3581	Mixed	2.9	2.6	3.3
Hosseini SY, 2010	2010	2004-2008	Urol oncol	Asia	Case Control	Ex smoker	3	6	Mixed	5.4	3.1	7.4
Hosseini SY, 2010	2010	2004-2008	Urol oncol	Asia	Case Control	Ever smoker	42	17	Mixed	5.5	3.1	7.7
Iscovich J, 1987	1987	1983-1985	Int J Cancer	Europe	Case Control	Ever smoker	91	144	Mixed	4.3	1.9	10.3
Iscovich J, 1987	1987	1983-1985	Int J Cancer	Europe	Case Control	Current smoker	54	52	Mixed	7.2	3.0	20.1
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Ex smoker	277	0	Males	1.8	1.4	2.2
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Current smoker	638	0	Males	2.0	1.7	2.5

Jensen OM, 1987	1987	1979-1981	J Epidemiol Community Health	Europe	Case Control	Ever smoker	115	210	Mixed	2.9	1.8	4.8
Karagas MR, 2005	2005	1994-1997	Cancer Lett	Americas	Case Control	Ever smoker	230	270	Males	1.4	0.90	2.1
Karagas MR, 2005	2005	1994-1997	Cancer Lett	Americas	Case Control	Ever smoker	54	110	Females	1.9	1.1	3.3
Kellen E, 2006	2006	1999-2004	Int J Cancer	Europe	Case Control	Ex smoker	112	182	Mixed	2.2	1.4	3.6
Kellen E, 2006	2006	1999-2004	Int J Cancer	Europe	Case Control	Current smoker	55	44	Mixed	6.0	3.3	11.0
Kunze E, 1991	1991	1977-1985	Cancer	Europe	Case Control	Ex smoker	531	531	Males	1.8	1.0	3.2
Kunze E, 1991	1991	1977-1985	Cancer	Europe	Case Control	Current smoker	531	531	Males	3.5	2.0	6.4
Lafuente A, 1996	1996	1993-1994	Br J Cancer	Africa	Cohort	Ever smoker	33	24	Mixed	1.3	0.59	2.8
Lin J, 2006	2006	1999-2006	Cancer	Americas	Case Control	Ever smoker	713	658	Mixed	2.3	1.8	2.9
Liu Y, 2012	2012	2007-2011	Oncol reports	Asia	Case Control	Ever smoker	214	609	Mixed	2.5	1.9	3.2
Lopez-Abente G, 1991	1991	1985-1986	Am J Epidemiol	Europe	Case Control	Ex smoker	90	196	Mixed	2.7	1.6	4.5
Lopez-Abente G, 1991	1991	1985-1986	Am J Epidemiol	Europe	Case Control	Ever smoker	396	618	Mixed	3.8	2.4	6.0
Lopez-Abente G, 1991	1991	1985-1986	Am J Epidemiol	Europe	Case Control	Current smoker	309	426	Mixed	4.4	2.8	7.0
Lopez-Abente G, 2001	2001	1985-86	J Epidemiol Community Health	Europe	Case Control	Ever smoker	30	57	Mixed	7.3	2.1	26.1
Malila N, 2006	2006	1984-1988	Eur J Cancer Prev	Europe	Case Control	Ever smoker	414	234	Mixed	1.8	1.6	2.0
Miller CT, 1978	1978	1977	J Chron Dis	Americas	Case Control	Ever smoker	136	0	Males	1.6	0.96	2.7
MILLS PK,	1991	1976-1982	Am J	Americas	Cohort	Ex smoker	19	0	Mixed	2.4	1.3	4.7

1991			Epidemiol									
MILLS PK, 1991	1991	1976-1982	Am J Epidemiol	Americas	Cohort	Current smoker	4	0	Mixed	5.7	1.7	18.6
Momas JP, 1994	1994	1987-1989	Eur J Epidemiol	Europe	Case Control	Ever smoker	159	399	Mixed	5.3	2.9	9.6
Mommsen S, 1983	1983	1977-1980	Eur J Cancer Clin Oncol	Europe	Case Control	Ever smoker	22	30	Females	1.9	0.90	3.9
Najem GR, 1982	1982	1978	In J Epidemiol	Americas	Case Control	Ever smoker	36	45	Mixed	2.0	1.1	3.7
Nomura A, 1989	1989	1977-1986	Am J Epidemiol	Americas	Case Control	Ever smoker	31	49	Females	1.6	0.80	3.0
Nomura A, 1989	1989	1977-1986	Am J Epidemiol	Americas	Case Control	Ever smoker	177	265	Males	4.8	2.7	8.2
Nordlund LA, 1997	1997	1964-1989	Int J cancer	Europe	Cohort	Current smoker	102	0	Females	2.3	1.4	3.8
Nordlund LA, 1997	1997	1964-1989	Int J cancer	Europe	Cohort	Ex smoker	102	0	Females	2.5	1.1	5.9
Pelucchi C, 2002	2002	1985-1992	Prev Med	Europe	Case Control	Ex smoker	5	18	Females	1.1	0.36	3.6
Pelucchi C, 2002	2002	1985-1992	Prev Med	Europe	Case Control	Ever smoker	47	73	Females	2.4	1.4	4.2
Pelucchi C, 2002	2002	1985-1992	Prev Med	Europe	Case Control	Current smoker	42	55	Females	2.9	1.6	5.1
Piper JM, 1986	1986	1975-1980	Am J Epidemiol	Americas	Case Control	Ever smoker	134	24	Females	2.4	1.5	4.0
Pitard A, 2001	2001	2001	CCC	Europe	Case Control	Ever smoker	1420	2895	Mixed	3.5	2.9	4.2
Pohlabeln H, 1999	1999	1989-1992	Eur J Epidemiol	Europe	Case Control	Current smoker	91	39	Mixed	5.2	2.7	9.7
Pommer W, 1999	1999	1990-1994	Nephrol Dial Transplant	Europe	Case Control	Ex smoker	180	209	Mixed	1.6	1.1	2.2
Pommer W, 1999	1999	1990-1994	Nephrol Dial Transplant	Europe	Case Control	Current smoker	253	144	Mixed	3.2	2.3	4.5
Puente D,	2006	1976-1996	CCC	Europe	Case	Ex smoker	2669	5381	Males	2.2	2.0	2.4

2006					Control							
Puente D, 2006	2006	1976-1996	CCC	Europe	Case Control	Ex smoker	309	739	Females	2.2	1.9	2.6
Puente D, 2006	2006	1976-1996	CCC	Europe	Case Control	Current smoker	611	973	Females	3.6	3.1	4.1
Puente D, 2006	2006	1976-1996	CCC	Europe	Case Control	Current smoker	3020	3759	Males	3.9	3.5	4.3
Quirk JT, 2004	2004	1982-1998	Tob Ind Dis	Americas	Case Control	Ex smoker	274	927	Mixed	2.1	1.6	2.7
Quirk JT, 2004	2004	1982-1998	Tob Ind Dis	Americas	Case Control	Ever smoker	396	1198	Mixed	2.4	1.9	3.0
Quirk JT, 2004	2004	1982-1998	Tob Ind Dis	Americas	Case Control	Current smoker	122	271	Mixed	3.4	2.5	4.6
Rebelakos A, 1985	1985	1980-1982	J Natl Cancer Institute	Europe	Case Control	Ex smoker	300	300	Mixed	2.0	1.2	3.3
Samanic C, 2006	2006	1998-2000	Cancer Epidemiol Biomarkers prev	Europe	Case Control	Ex smoker	6	6	Females	1.8	0.50	7.2
Samanic C, 2006	2006	1998-2000	Cancer Epidemiol Biomarkers prev	Europe	Case Control	Ever smoker	27	12	Females	3.3	1.3	8.0
Samanic C, 2006	2006	1998-2000	Cancer Epidemiol Biomarkers prev	Europe	Case Control	Ex smoker	453	464	Males	3.8	2.8	5.3
Samanic C, 2006	2006	1998-2000	Cancer Epidemiol Biomarkers prev	Europe	Case Control	Ever smoker	950	782	Males	5.1	3.7	7.0
Samanic C, 2006	2006	1998-2000	Cancer Epidemiol Biomarkers prev	Europe	Case Control	Current smoker	21	6	Females	5.1	1.6	16.4

Samanic C, 2006	2006	1998-2000	Cancer Epidemiol Biomarkers prev	Europe	Case Control	Current smoker	492	314	Males	7.4	5.3	10.4
Schifflers E, 1987	1987	1984-1985	Int J Cancer	Europe	Case Control	Ever smoker	74	74	Mixed	5.3	1.6	18.1
Shakhssalim, 2010	2010	2005-2006	Asian Pac J Cancer Prev	Asia	Case Control	Ever smoker	399	627	Mixed	2.0	1.5	2.6
Shankar A, 2007	2007	1993-1998	Eur J Cancer	Asia	Cohort	Ex smoker	146	0	Mixed	2.7	1.4	5.2
Siemiatycki J, 1994	1994	1979-1984	Epidemiology	Americas	Case Control	Ever smoker	844	1371	Mixed	15.8	8.7	29.1
Siemtiatycki J, 1995	1995	1979-1985	In J Epidemiol	Americas	Case Control	Ever smoker	441	0	Mixed	2.4	1.6	3.6
Slattery ML, 1988	1988	1977-1983	Cancer	Americas	Case Control	Current smoker	91	111	Males	3.7	2.6	5.3
Steineck G, 1988	1988	1967-1968	Acta Oncologica	Europe	Cohort	Ever smoker	54	0	Mixed	1.9	0.80	4.7
Terry PD, 2006	2006	2005	Int j cancer	Americas	Case Control	Ex smoker	138	110	Mixed	3.2	1.9	5.4
Terry PD, 2006	2006	2005	Int j cancer	Americas	Case Control	Current smoker	60	26	Mixed	6.3	3.3	12.0
Tulinus H, 1997	1997	1967-1991	Cancer Epidemiol Biomarkers prev	Europe	Cohort	Ex smoker	167	0	Males	2.3	1.4	3.9
Vineis P, 1988	1988	1977-1983	Cancer res	Europe	Case Control	Ex smoker	22	62	Mixed	2.1	1.1	4.0
Vineis P, 1988	1988	1977-1983	Cancer res	Europe	Case Control	Ex smoker	30	45	Mixed	2.5	1.3	5.0
Vineis P, 1988	1988	1977-1983	Cancer res	Europe	Case Control	Current smoker	151	127	Mixed	5.5	3.2	9.5
Vineis P, 1988	1988	1977-1983	Cancer res	Europe	Case Control	Current smoker	65	47	Mixed	6.2	3.3	11.7
Vizcaino AP,	1994	1963-1977	CCC	Africa	Case	Ex smoker	2	60	Mixed	0.30	0.10	1.4

1994					Control							
Vizcaino AP, 1994	1994	1963-1977	CCC	Africa	Case Control	Current smoker	142	1117	Mixed	1.1	0.80	1.4
Wakai K, 1993	1993	1976-1978	Jpn J Cancer Res	Asia	Cohort	Ever smoker	175	0	Males	0.88	0.45	1.7
Yun YH, 2005	2005	1996-2000	Cancer Detect Prev	Asia	Cohort	Ex smoker	52	0	Mixed	0.96	0.65	1.4
Yun YH, 2005	2005	1996-2000	Cancer Detect Prev	Asia	Cohort	Current smoker	137	0	Mixed	2.2	1.5	3.4
Zarzour AH, 2008	2008	2005	BMC cancer	Africa	Case Control	Ever smoker	130	260	Mixed	5.3	3.2	8.7
Zeegers MPA, 2002	2002	1986-1992	CCC	Europe	Cohort	Ex smoker	263	0	Mixed	2.1	1.5	3.0
Zeegers MPA, 2002	2002	1986-1992	CCC	Europe	Cohort	Current smoker	282	0	Mixed	3.3	2.4	4.0
Zhang ZF, 1994	1994	1972-1980	Cancer Epidemiol Biomarkers prev	Americas	Cohort	Ever smoker	77	0	Mixed	1.7	0.70	4.0
Zheng YL, 2012	2012	2006-2010	Cancer Epidemiol Biomarkers prev	Africa	Case Control	Ex smoker	114	280	Males	1.2	0.90	1.7
Zheng YL, 2012	2012	2006-2010	Cancer Epidemiol Biomarkers prev	Africa	Case Control	Current smoker	525	908	Males	2.1	1.7	2.6

Supplementary table 1b All study data for Bladder Cancer Mortality

Author	Year	Years of follow up	Journal	Region	Study Design	Risk group	Cases	Controls	Gender	Risk effect	Lower CI	Upper CI
Fleshner N,	1999	1995-1995	Cancer	Americas	Cohort	Ex smoker	51	0	Mixed	0.99	0.77	1.3

1999												
Fleshner N, 1999	1999	1995-1995	Cancer	Americas	Cohort	Current smoker	108	0	Mixed	1.4	1.0	1.9
Freedman ND, 2011	2011	1995-1996	JAMA	Europe	Cohort	Ex smoker	2483	0	Males	2.1	1.9	2.4
Freedman ND, 2011	2011	1995-1996	JAMA	Americas	Cohort	Current smoker	206	0	Females	4.7	3.7	5.8
Freedman ND, 2011	2011	1995-1996	JAMA	Americas	Cohort	Current smoker	809	0	Females	2.5	2.1	3.1
Freedman ND, 2011	2011	1995-1996	JAMA	Americas	Cohort	Ex smoker	288	0	Males	3.9	3.5	4.4
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Current smoker	105	0	Males	1.9	1.2	3.0
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Ex smoker	50	0	Males	1.6	0.90	2.6
Kurahashi N, 2009	2009	1990-1993	Cancer Sci	Asia	Cohort	Ex smoker	42	0	Mixed	1.3	0.78	2.1
Kurahashi N, 2009	2009	1990-1993	Cancer Sci	Asia	Cohort	Current smoker	92	0	Mixed	1.5	0.92	2.3
McCormack VA, 2010	2010	1991-1998	Int J Cancer	Europe	Cohort	Ever smoker	349	0	Mixed	2.9	2.3	3.7
Nilsson S, 2001	2001	1960-1996	J Epidemiol Community Health	Europe	Cohort	Ex smoker	2	0	Females	1.0	0.24	4.2
Nilsson S, 2001	2001	1960-1996	J Epidemiol Community Health	Europe	Cohort	Current smoker	9	0	Females	1.4	0.67	2.9
Nilsson S, 2001	2001	1960-1996	J Epidemiol Community Health	Europe	Cohort	Ex smoker	29	0	Males	2.2	1.3	3.7
Nilsson S, 2001	2001	1960-1996	J Epidemiol Community Health	Europe	Cohort	Current smoker	25	0	Males	2.2	1.2	3.9
Rink M, 2012	2012	1987-2007	Eur Urol	Americas	Cohort	Ex smoker	956	0	Mixed	1.1	0.86	1.4
Rink M, 2012	2012	1987-2007	Eur Urol	Americas	Cohort	Current	593	0	Mixed	1.1	0.85	1.5

						smoker						
Sfakianos JP, 2011	2011	1994-2008	BJU Int	Americas	Cohort	Ever smoker	483	0	Mixed	1.1	0.79	1.6
Wen CP, 2004	2004	1982-1992	Prev Med	Asia	Cohort	Current smoker	15	0	Males	1.7	0.65	4.5

Supplementary table 1c All study data for Renal Cell Cancer Incidence

Author	Year	Years of follow up	Journal	Region	Study Design	Risk Group	Cases	Controls	Gender	Risk effect	Lower CI	Upper CI
Brennan P, 2008	2008	1999-2003	Br J Cancer	Europe	Case Control	Current smoker	333	521	Mixed	0.87	0.71	1.1
Brennan P, 2008	2008	1999-2003	Br J Cancer	Europe	Case Control	Ex smoker	251	353	Mixed	0.88	0.71	1.1
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Ever smoker	53	259	Females	1.2	0.80	1.8
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Current smoker	92	574	Females	1.4	0.90	2.3
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Ever smoker	202	1068	Males	1.8	1.3	2.7
Chiu BC, 2001	2001	1986-1989	Ann Epidemiol	Americas	Case Control	Current smoker	40	435	Males	2.1	1.3	3.2
Engeland A, 1996	1996	1964-1965	CCC	Europe	Cohort	Ex smoker	1	0	Females	1.1	0.60	2.0
Engeland A, 1996	1996	1964-1965	CCC	Europe	Cohort	Ex smoker	28	0	Males	1.3	0.80	2.4
Flaherty KT, 2005	2005	1976-2000	CCC	Americas	Cohort	Current smoker	22	0	Females	0.90	0.60	1.5
Flaherty KT, 2005	2005	1976-2000	CCC	Americas	Cohort	Ex smoker	68	0	Females	1.3	0.90	1.8
Flaherty KT, 2005	2005	1976-2000	CCC	Americas	Cohort	Ex smoker	62	0	Males	1.4	0.90	2.2

Flaherty KT, 2005	2005	1976-2000	CCC	Americas	Cohort	Current smoker	8	0	Males	1.3	0.60	2.9
Goodman MT, 1986	1986	1977-1983	Am J Epidemiol	Americas	Case Control	Ever smoker	145	142	Mixed	1.1	0.67	1.8
Hu J, 2005	2005	1994-1997	Eur J Cancer	Americas	Case Control	Current smoker	113	558	Males	0.90	0.70	1.2
Hu J, 2005	2005	1994-1997	Eur J Cancer	Americas	Case Control	Ex smoker	386	1354	Males	1.2	1.0	1.5
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Current smoker	324	0	Males	1.3	1.0	1.5
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Ex smoker	194	0	Males	1.2	0.90	1.6
Kreiger N, 1991	1991	1986-86	CCC	Americas	Case Control	Ever smoker	114	306	Females	1.9	1.3	2.6
Kreiger N, 1991	1991	1986-86	CCC	Americas	Case Control	Ever smoker	245	449	Males	2.0	1.4	2.8
Kreiger N, 1991	1991	1986-86	CCC	Americas	Case Control	Current smoker	67	158	Females	2.2	1.5	3.2
Kreiger N, 1991	1991	1986-86	CCC	Americas	Case Control	Current smoker	102	174	Males	2.3	1.5	3.4
La Vecchia C, 1990	1990	1985-1990	Cancer Res	Europe	Case Control	Ex smoker	32	96	Mixed	1.7	1.0	3.1
McCredie M, 1992	1992	1989-1990	Eur J Cancer	Oceania	Case Control	Ex smoker	110	0	Mixed	1.4	1.0	2.0
McCredie M, 1992	1992	1989-1990	Eur J Cancer	Oceania	Case Control	Current smoker	83	0	Mixed	2.2	1.6	3.0
McLaughlin JK, 1984	1984	1974-1979	J Natl Cancer Inst	Americas	Case Control	Ever smoker	148	171	Males	1.7	1.1	2.6
McLaughlin JK, 1984	1984	1974-1979	J Natl Cancer Inst	Americas	Case Control	Ever smoker	89	92	Females	1.9	1.3	3.1
McLaughlin JK, 1990	1990	1954-1980	Public Healh Rep	Americas	Cohort	Ex smoker	111	0	Mixed	1.1	0.85	1.4
McLaughlin JK, 1990	1990	1954-1980	Public Healh Rep	Americas	Cohort	Current smoker	284	0	Mixed	1.5	1.2	1.8
McLaughlin	1992	1987-1989	Int J Cancer	Asia	Case	Ever	67	57	Mixed	2.3	1.1	4.9

JK, 1992					Control	smoker						
McLaughlin JK, 1995	1995	1989-1991	Int J cancer	Americas	Case Control	Ex smoker	545	762	Mixed	1.2	1.0	1.4
McLaughlin JK, 1995	1995	1989-1991	Int J cancer	Americas	Case Control	Ever smoker	1083	1354	Mixed	1.3	1.1	1.5
McLaughlin JK, 1995	1995	1989-1991	Int J cancer	Americas	Case Control	Current smoker	538	592	Mixed	1.4	1.2	1.7
Mellemgaard A, 1994	1994	1989-1991	CCC	Europe	Case Control	Ex smoker	82	89	Males	1.0	0.50	2.0
Mellemgaard A, 1994	1994	1989-1991	CCC	Europe	Case Control	Current smoker	48	52	Females	1.1	0.60	2.0
Mellemgaard A, 1994	1994	1989-1991	CCC	Europe	Case Control	Current smoker	96	92	Males	1.1	0.60	2.1
Mellemgaard A, 1994	1994	1989-1991	CCC	Europe	Case Control	Ex smoker	34	34	Females	1.2	0.70	2.3
Muscat JE, 1995	1995	1973-1991	Cancer	Americas	Case Control	Ex smoker	200	226	Males	0.90	0.70	1.5
Muscat JE, 1995	1995	1973-1991	Cancer	Americas	Case Control	Current smoker	70	135	Females	1.0	0.70	1.6
Muscat JE, 1995	1995	1973-1991	Cancer	Americas	Case Control	Ex smoker	50	50	Females	1.1	0.70	1.7
Muscat JE, 1995	1995	1973-1991	Cancer	Americas	Case Control	Current smoker	174	128	Males	1.4	1.0	2.0
Nordlund LA, 1997	1997	1964-1989	Int J cancer	Europe	Cohort	Current smoker	94	0	Females	1.1	0.59	2.0
Nordlund LA, 1997	1997	1964-1989	Int J cancer	Europe	Cohort	Ex smoker	94	0	Females	1.9	0.75	4.7
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Ex smoker	426	798	Mixed	0.90	0.80	1.1
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Ex smoker	73	798	Mixed	0.90	0.60	1.2
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Current smoker	17	785	Mixed	0.70	0.40	1.3
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case	Current	430	785	Mixed	1.1	0.70	1.6

					Control	smoker						
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Ex smoker	117	798	Mixed	1.2	0.90	1.6
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Ex smoker	19	798	Mixed	0.60	0.20	1.8
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Current smoker	104	785	Mixed	1.2	0.70	2.1
Purdue, 2013	2013	2002-2007	Int J Cancer	Americas	Case Control	Current smoker	69	785	Mixed	1.2	0.70	2.1
Schlehofer B, 1995	1995	1989-1991	Int J Epidemiol	Europe	Case Control	Ex smoker	14	14	Females	0.99	0.43	1.4
Schlehofer B, 1995	1995	1989-1991	Int J Epidemiol	Europe	Case Control	Current smoker	18	21	Females	0.83	0.39	1.8
Schlehofer B, 1995	1995	1989-1991	Int J Epidemiol	Europe	Case Control	Ex smoker	70	80	Males	1.1	0.63	1.9
Schlehofer B, 1995	1995	1989-1991	Int J Epidemiol	Europe	Case Control	Current smoker	81	70	Males	1.4	0.82	2.5
Setiawan VW, 2007	2007	1993-1996	Am J Epi	Americas	Cohort	Ex smoker	42	0	Females	1.3	0.90	2.0
Setiawan VW, 2007	2007	1993-1996	Am J Epi	Americas	Cohort	Ex smoker	119	0	Males	1.5	1.1	2.1
Setiawan VW, 2007	2007	1993-1996	Am J Epi	Americas	Cohort	Current smoker	22	0	Females	1.7	1.0	2.8
Setiawan VW, 2007	2007	1993-1996	Am J Epi	Americas	Cohort	Current smoker	53	0	Males	2.3	1.6	3.4
Sharpe CR, 1989	1989	1987	CMAJ	Americas	Case Control	Current smoker	26	42	Mixed	0.53	0.30	0.95
Sharpe CR, 1989	1989	1987	CMAJ	Americas	Case Control	Ex smoker	104	106	Mixed	0.90	0.57	1.5
Siemtiatycki J, 1995	1995	1979-1985	In J Epidemiol	Americas	Case Control	Ever smoker	143	0	Mixed	1.0	0.70	1.6
Talamini R, 1990	1990	1986-1989	CCC	Europe	Case Control	Ex smoker	55	161	Mixed	1.4	0.83	2.2
Wang G,	2012	2007-2009	Cancer	Asia	Case	Ever	74	85	Mixed	0.95	0.63	1.4

2012			Epidemiol		Control	smoker						
Yu MC, 1986	1986	1975-1979	J Natl Cancer Inst	Americas	Case Control	Ever smoker	33	32	Females	1.1	0.50	2.4
Yu MC, 1986	1986	1975-1979	J Natl Cancer Inst	Americas	Case Control	Ever smoker	88	75	Males	2.1	1.1	4.4
Yuan JM, 1998	1998	1986-1994	Cancer Epidemiol Biomarkers prev	Americas	Case Control	Ex smoker	463	450	Mixed	1.2	1.0	1.5
Yuan JM, 1998	1998	1986-1994	Cancer Epidemiol Biomarkers prev	Americas	Case Control	Ever smoker	800	713	Mixed	1.4	1.1	1.6
Yuan JM, 1998	1998	1986-1994	Cancer Epidemiol Biomarkers prev	Americas	Case Control	Current smoker	337	262	Mixed	1.5	1.2	1.9
Yun YH, 2005	2005	1996-2000	Cancer Detect Prev	Asia	Cohort	Current smoker	106	0	Mixed	0.94	0.66	1.3
Yun YH, 2005	2005	1996-2000	Cancer Detect Prev	Asia	Cohort	Ex smoker	42	0	Mixed	1.3	0.80	2.1

Supplementary table 1d All study data for Renal Cell Cancer Mortality

Author	Year	Years of follow up	Journal	Region	Study Design	Risk group	Cases	Controls	Gender	Risk effect	Lower CI	Upper CI
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Current smoker	90	0	Males	1.0	0.70	1.5
Jee SH, 2004	2004	1992-1995	CCC	Asia	Cohort	Ex smoker	56	0	Males	1.2	0.80	1.9
McCormack VA, 2010	2010	1991-1998	Int J Cancer	Europe	Cohort	Ever smoker	117	0	Mixed	1.3	0.90	1.8
Parker A, 2008	2008	1970-2002	Int J Urol	Americas	Cohort	Ex smoker	2242	0	Mixed	0.93	0.79	1.1

Parker A, 2008	2008	1970-2002	Int J Urol	Americas	Cohort	Current smoker	2242	0	Mixed	1.3	1.1	1.6
Sweeney C, 2000	2000	1995-1997	Epidemiology	Americas	Cohort	Current smoker	62	0	Mixed	1.7	1.2	2.5
Sweeney C, 2000	2000	1995-1997	Epidemiology	Americas	Cohort	Ex smoker	185	0	Mixed	1.2	0.80	1.7
Wen CP, 2004	2004	1982-1992	Prev Med	Asia	Cohort	Current smoker	9	0	Males	1.6	0.59	4.6

Supplementary Table 2 Pooled relative risks (RRs) and 95% confidence intervals (CIs) for incidence from Bladder Cancer in smokers of non-cigarette tobacco.

Non-cigarette tobacco product	Incidence		
	No. of studies	Pooled RR (95% CI)	I^2 (p for heterogeneity)
Cigars	4	1.62 (1.18-2.22)	39.4% (0.2)
Pipes	4	1.49 (1.18-1.88)	0.0% (0.6)
Snuff	2	0.89 (0.56-1.42)	23.7% (0.6)
Cigarillos	1	1.00 (0.41-2.50)	--
Chewing	2	1.04 (0.75-1.45)	0.0% (0.9)

*Revision notes

Re-revision Notes

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European Urology
Editorial Office

Dear Editorial office,
Re: **The role of tobacco smoke in bladder and kidney carcinogenesis: A comparison of exposures and meta-analysis of incidence and mortality risks**
Thank you for taking the time to review our revised manuscript. We believe we have overcome the remaining key concerns raised by the editorial team and have addressed each reviewer comment in detail (please see below). We thank you for your time and consideration.

Yours sincerely,
Marcus Cumberbatch

Comments to Author:

Reviewer #3: I have only three small grammatical comments at this point:

On line 379, please change to "non muscle-invasive (NMIBC) versus muscle-invasive bladder cancer (MIBC).
Line 386, change "our" to "out"
Would consider flip flopping the last two sentences in the conclusions as the last sentence is not a strong ending (lines 397 to 401).

This has been done.

Reviewer #5: EUROPEAN UROLOGY STATISTICAL REVIEW

Minor comments
1) Please follow the European Urology guidelines for presentation of statistics:
http://www.europeanurology.com/article/S0302-2838(14)00598-3/pdf/guidelines-for-reporting-of-

statistics-in-european-urology. In particular, precision is often misreported. P values are often given categorically (e.g. p<0.05) or to inappropriate precision (e.g. p=0.59). Estimates are reported to extremely different levels of precision in supplementary table 1a.
2) Report p values for the main hypotheses, which are whether tobacco influences risk.
3) Is opium tobacco?
4) Line 233: the ".0" in the p value of 1.0 is somewhat redundant.
5) Line 235 and 247: you are accepting the null hypothesis (guideline 3.1)

This has been done.

Major comments

1) Do not report I2. I am aware that this is commonly reported, but is, in my view, invalid. I2 should either by 0 (there isn't heterogeneity) or 1 (there is heterogeneity); the only reason it is not 1 or 0 is inadequate sample size. The I2 statistics are all very large here because sample sizes are large. Instead of this statistic, report a p value for heterogeneity. However, and this is the critical point, don't just report "heterogeneity / no heterogeneity" and be done with it. You have to investigate sources of heterogeneity and come to some scientific conclusions about what it means.

We disagree on this point. The I^2 heterogeneity statistic does not depend only on the number of studies included in the meta-analysis. It is in fact true that with a small number of studies statistically significant heterogeneity would be evident only when the heterogeneity is high. With a high number of studies it is more likely to find a significant heterogeneity, but this is not a rule, and the I^2 could be 0 as well as 10 or 50%. We would prefer to keep them, as in other meta-analyses published by European Urology (please see *'A Systematic Review and Meta-analysis of Tobacco Use and Prostate Cancer Mortality and Incidence in Prospective Cohort Studies'* by Islami et al: URL: http://www.ncbi.nlm.nih.gov/pubmed/25242554). This gives to the reader a useful measure to interpret the findings.
We have tried to investigate, and discuss, potential sources of heterogeneity by undertaking stratified analyses by sex and geographical area of the studies, two of the most consistently reported data across studies. Since this is a meta-analysis of published

data, we were however unable to identify other potential modifier effects since not consistently reported across studies. However, when possible we used the maximally adjusted estimates for the meta-analysis in order to reduce the risk of possible unmeasured confounding (lines 161-164).

2) The authors conduct subgroup analyses rather than interaction analyses (see guideline 3.5). We are not interested in the estimate of the effects of smoking in men and then separately in women; we want to know whether the effects of smoking differ between men and women. Similarly, we don't want to know the risk estimates separately for cigars, snuff etc. etc. but whether these are higher or lower than for cigarettes.

We agree with the reviewer. Since we are not dealing with original but with published data, in meta-analysis settings the possible interaction effect can be tested by comparing pooled risk estimates across strata of a possible modifier effect. In the current version of the manuscript we provided in the text the p-values for the difference of pooled RR across sex, geographical area and type of smoking (non-cigarette vs sigarette tobacco).