

## Quantified relations between exposure to tobacco smoking and bladder cancer risk

Van Osch, Frits; Jochems, Sylvia; van Schooten, Frederik J; Bryan, Richard; Zeegers, Maurice

DOI:

[10.1093/ije/dyw044](https://doi.org/10.1093/ije/dyw044)

License:

Other (please specify with Rights Statement)

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Van Osch, F, Jochems, S, van Schooten, FJ, Bryan, R & Zeegers, M 2016, 'Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies', *International Journal of Epidemiology*. <https://doi.org/10.1093/ije/dyw044>

[Link to publication on Research at Birmingham portal](#)

### **Publisher Rights Statement:**

This is a pre-copyedited, author-produced PDF of an article accepted for publication in *International Journal of Epidemiology* following peer review. The version of record 'Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies' is available online at: <http://dx.doi.org/10.1093/ije/dyw044>  
Checked for eligibility: 09/03/2016

### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### **Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

# **Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies**

Frits H.M. van Osch\* (1, 2), Sylvia H.J. Jochems (1, 2), Frederik-Jan van Schooten (3)  
Richard T. Bryan (2), Maurice P. Zeegers (1)

1. Department of Complex Genetics, NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands
2. School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom
3. Department of Pharmacology and Toxicology, NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands

## **Abstract**

### **Background:**

Smoking is a major risk factor for bladder cancer (BC). This meta-analysis updates previous reviews on smoking characteristics and BC risk, and provides a more quantitative estimation of the dose-response relationship between smoking characteristics and BC risk.

### **Methods:**

In total, 89 studies comprising data from 57 145 BC cases were included and summary odds ratios (SORs) were calculated. Dose-response meta-analyses modelled relationships between smoking intensity, duration, pack-years and cessation and BC risk. Sources of heterogeneity were explored and sensitivity analyses were conducted to test the robustness of findings.

### **Results:**

Current smokers (SOR=3.14, 95% CI=2.53-3.75) and former smokers (SOR=1.83, 95% CI=1.52-2.14) had an increased risk of BC compared to never smokers. Age at first exposure was negatively associated with BC risk. BC risk increased gradually by smoking duration and a risk plateau at smoking 15 cigarettes a day and 50 pack-years was observed. Smoking cessation is most beneficial from 20 years before diagnosis. The population attributable risk of BC for smokers has decreased from 50% to 43% in men and from 35% to 26% in women from Europe since estimated in 2000. Results were homogenous between sources of heterogeneity, except for lower risk estimates found in studies of Asian populations.

### **Conclusions:**

Active smokers are at an increased risk of BC. Dose-response meta-analyses showed a BC risk plateau for smoking intensity and indicate that even after long-term smoking cessation, an elevated risk of bladder cancer remains.

**Key words**

Bladder cancer incidence; smoking; meta-analysis; dose-response analyses; observational studies; population attributable risk

**Key messages**

- This large meta-analysis confirms smoking as a major risk factor for bladder cancer.
- A risk plateau is observed at smoking 15 cigarettes a day and a 50% increased bladder cancer risk remains after long-term smoking cessation
- The population attributable risk of bladder cancer for smoking has decreased in Europe since 2000 because of a smaller number of smokers population wide

## **BACKGROUND**

Bladder cancer (BC) is estimated to be the ninth most incident cancer worldwide, with around 400 000 new cases per year; the disease accounts for a larger share of total cancer incidence in more developed regions (1). Cigarette smoking is a major risk factor for urothelial cell carcinoma (which also includes cancers of the renal pelvis and ureter) (2). Since recent studies estimated 22.8% of Europeans (3), 18.1 % of North Americans (4) and 52.9% of males from China (5) smoke, it is expected to remain an important BC risk factor in the near future. Studies investigating the association between smoking and BC risk were summarized in a meta-analysis 15 years ago (2) and several systematic reviews (6-8). However, further relevant studies have emerged since these reviews, allowing for more robust estimates, more detailed subgroup analyses, quantification of BC risk by dose-response investigations.

According to age- and gender-adjusted estimates from an earlier meta-analysis, those patients smoking at diagnosis (current smokers) had a 3.33 fold increased risk of developing BC compared to never smokers, and for former smokers the summary odds ratio (SOR) was 1.98; these age-adjusted risk estimates were comparable between males and females (2). Furthermore, BC risk increased with the amount of cigarettes smoked per day and the number of years of smoking, although this was only assessed in a dichotomous way (e.g. 1-20 cigarettes per day vs. >20 cigarettes per day) in this meta-analysis (2).

The aim of this study was to provide an up-to-date estimation of the role of smoking in BC risk and to gain a more detailed quantification on several smoking characteristics (i.e. smoking intensity, duration and cessation) by performing dose-response meta-analyses.

## **METHODS**

### **Search strategy**

Both Medline and Embase online databases were used to search for epidemiologic studies on cigarette smoking and BC incidence. The search included the (MeSH) search terms “urinary bladder neoplasms”, “incidence” “risk”, “smoking” and “epidemiologic studies” in different combinations and resulted in a total count of 2 112 articles after removal of duplicates. Publications were excluded if they did not involve humans. Publications that did not provide useable data to calculate risk estimates and the associated 95% confidence intervals for smoking characteristics and BC incidence were excluded. Included publications provided risk estimates for at least one of the selected cigarette smoking characteristics, including: smoking status (never, former, current), age at first exposure, daily cigarette consumption (intensity), duration of cigarette consumption, number of smoking pack-years and number of years since cessation. Publications reporting only on ever versus never smokers were excluded. Where a single study was described in several publications, the most recent publication was used for analysis.

### **Data collection**

The Newcastle-Ottawa Scale (NOS) scale (9) was used to assess study quality and to extract information on possible sources of heterogeneity within individual publications by two of the authors (FvO and SJ). Information on the following variables was extracted and numerated in a dataset: year of publication, country and geographic area (North America, Europe, Asia, Africa, South America), anatomic site (bladder, upper tract urothelium, renal pelvis), cigarette smoking assessment (interview or questionnaire), case and control source (hospital, population or both) and factors adjusted for in the analysis. The association between smoking and BC risk is expressed in odds ratios (ORs) for both case-control studies and cohort studies

included in this review. Where possible, risk estimate data was extracted directly from included articles and included both unadjusted and adjusted estimates. When direct risk estimates were not available, two-way contingency tables were constructed separately and unadjusted ORs and 95% confidence intervals were calculated. Since age and gender are considered to be major confounders of the association between smoking and BC, all included adjusted risk estimates adjusted for at least age and gender. For smoking duration, intensity, pack-years and cessation, risk estimates for smoking and BC risk were recorded per category, for example per 10 years of smoking duration, when data was available. Publications were excluded if the number of cases and/or controls or the number of person-years were not given.

### **Statistical analysis**

In order to investigate publication bias, funnel plots were constructed, plotting the logarithmically transformed ORs against the standard error of the associated  $\log(\text{OR})$  (10). The distribution of study risk estimates across the funnel plot was examined visually and Egger's test for small study effects was performed to assess the degree of asymmetry (10). A random effects model was employed in all meta-analysis procedures. Between-study variance was estimated by  $I^2$  and subgroup analyses. Stata statistical software was used for all analyses (version 13; Stata Corp., College Station, TX).

Summary ORs were estimated using classical meta-analysis for smoking status, age at first exposure ( $>20$  years versus  $\leq 20$  years) and these results were obtained separately for men and women if data were available from the included publications. A cumulative meta-analysis was performed in order to investigate whether the association between smoking and BC incidence varied in time. Subgroup analyses were performed to explore differences in risk estimates between possible sources of heterogeneity, including geographic area, anatomic

site, case and control source, study design and smoking assessment. The association of smoking duration, intensity, pack-years and cessation with BC risk was examined using a dose-response meta-analysis. The assigned dose for the dose-response analysis was determined by taking the median of each category (e.g. 15 cigarettes for category 10-20 cigarettes per day). Dose-response trends were estimated using both the variance weighted least squares (VWLS) and generalized least squares (GLS) regression methods (11). Since GLS is the most robust method with regard to inevitable covariance between study observations in a meta-analysis, the results from the GLS method are presented. Restricted cubic splines, which set knots at the 5<sup>th</sup>, 35<sup>th</sup>, 65<sup>th</sup> and 95<sup>th</sup> percentile, were used to investigate statistical non-linearity for all curves. Finally, population attributable risk (PAR) of BC for current smokers compared to never smokers was estimated for Europe, North America and China using the overall pooled risk estimates obtained by all included studies and the most recent estimates of proportions of smokers in these populations.

## RESULTS

### Study characteristics

For this meta-analysis, 99 articles that discussed cigarette smoking and BC incidence were identified between 1968 and 2015 based on their abstract. After full text evaluation, 89 articles were included for full analysis (**Figure 1**). Study characteristics including year of publication, country, case/control source, smoking assessment and anatomic site are summarized in **Table 1**. Six articles were excluded after full-text evaluation due to insufficient NOS score, duplicate populations in several articles or not being published in English (101-106). Furthermore, three articles only presented data on ever smokers, as opposed to current and former smokers (107-109), and one cohort study did not present 95% confidence intervals and omitted the case-control data to calculate these (110). (**FIGURE 1 HERE**)

Of the 89 included studies, 72 were case-control studies (12-27, 29, 30, 32-38, 40-42, 44-49, 51, 53-65, 68, 70-73, 76, 77, 79, 81-87, 89, 90, 92, 93, 95-99) and 17 were cohort studies (28, 31, 39, 43, 50, 52, 66, 67, 69, 74, 75, 78, 80, 88, 91, 94, 100). Three articles presented risk estimates from different study populations and were considered as separate studies in the analysis (9, 78, 84). In the case-control studies, cases were identified from hospitals (n=46) (13-15, 17-23, 26, 29, 33-38, 40, 41, 46, 49, 53, 54, 57, 58, 64, 65, 70-73, 76, 77, 81, 83, 85, 86, 89, 90, 93, 96-99) or in predefined populations (n=24) (16, 24, 25, 27, 32, 35, 42, 47, 48, 55, 56, 59-63, 68, 79, 82, 84, 87, 92, 95), and two studies used both hospital- and population-based cases (12, 30). Thirty-nine of the case-control studies recruited controls from hospitals (12-14, 16, 17, 19, 21-24, 26, 29, 33-37, 40, 41, 44-46, 49, 50, 53, 54, 57, 58, 63-65, 68, 70, 71, 73, 74, 76-79, 81-83, 85-87, 89, 91-93, 96, 97, 99) and thirty-three case-control studies recruited population controls (15, 18, 20, 25, 27, 30, 32, 35, 38, 42, 45, 47, 48, 51, 52, 55-57,

59, 61-63, 68, 70, 72, 79, 82, 84, 87, 90, 92, 95, 98). Detailed information on cigarette smoking habits was assessed by interview (n=62) (12-18, 21, 23, 25-27, 29, 30, 32-38, 40-46, 48, 49, 51, 53-55, 58, 59, 61, 62, 64, 65, 70, 72, 73, 77, 79, 81-87, 89, 90, 92, 93, 95-99), questionnaire (n=26) (19, 20, 24, 28, 31, 39, 47, 52, 56, 57, 60, 63, 66-69, 71, 74-76, 78, 80, 88, 91, 94, 100), and medical records (n=1) (50). **(TABLE 1 HERE)**

### **Publication bias and heterogeneity**

Some publication bias seemed to be present, as judged from funnel plots for current smoking risk estimates in studies that present unadjusted ORs (n=45). Publication bias seemed to be of less importance in studies presenting age and sex adjusted (n=11) and multiple-adjusted (n=13) ORs. Egger's test for small study effects demonstrated that no small studies remained unpublished (p=0.150). Judging from  $I^2$  statistics there may have been heterogeneity (most  $I^2$  values between 70% and 90% for both classical- and dose-response meta-analyses), however when assessing heterogeneity in subgroup analyses (**Figure 2**) there did not seem to be any substantial heterogeneity. **(FIGURE 2 HERE)**

### **Risk estimates from classical meta-analysis**

**Table 2** summarizes both unadjusted and adjusted estimates for smoking status and age at first exposure obtained from the classical meta-analysis. The adjusted SOR for current smokers compared to never smokers was 3.14 (95% CI, 2.53-3.75). Former smokers had a 1.78 (95% CI, 1.53-2.03)-fold increased risk of developing BC compared to never smokers. This association was comparable between men (3.44, 95% CI=2.67-4.22) and women (3.56, 95% CI=2.76-4.36). When investigating all obtained estimates, the observed SORs remained comparable to the adjusted estimates.

For age at first exposure, 5 male-only studies presenting age-adjusted risk estimates were pooled which resulted in a SOR of 1.36 (95% CI=0.91-1.80) comparing males who started

smoking before the age of 20 to those who had started smoking after the age of 20. Unadjusted SORs showed no effect of age at first exposure in females (0.99, 95% CI=0.31-1.68) as opposed to stronger associations for males only (1.34, 95% CI=1.02-1.68) and studies including both sexes (1.30, 95% CI=1.13-1.47). **(TABLE 2 HERE)**

### **Risk estimates from dose-response meta-analysis**

Dose-response curves estimated from studies reporting on smoking intensity (n=23) (25, 30, 33-35, 37-40, 45-48, 57, 62, 67, 71, 78, 81, 82, 92, 99), pack-years (n=8) (34, 50, 61, 71-73, 82, 94), duration (n=15) (25, 30, 38, 39, 47, 53, 59, 62, 67, 71, 75, 82, 92, 96, 99) and cessation (n=7) (25, 33, 38, 67, 72, 92, 94) and BC risk are depicted in **Figure 3**. The shape of both the intensity and pack-years curves is reminiscent of a logarithmic curve, showing a rapid increase of BC risk before declining at a certain point. For intensity, BC risk increases only marginally from smoking more than 15 cigarettes a day, and likewise for pack-years from 50 pack-years onwards. The risk of BC increases almost linearly increases by smoking duration in years, although statistical tests for non-linearity showed that it is non-linear ( $p < 0.05$  at all investigated knots). Those who stopped smoking more than 25 years prior to diagnosis were approximately at a 1.5 fold higher risk of BC compared to never smokers, whereas those who stopped smoking between 5 and 15 years prior to diagnosis were at a two- to threefold increased risk of BC compared to never smokers. There is a slight stagnation around 10 years of cessation, indicating a relatively small risk reduction between 5 and 15 years of smoking cessation. **(FIGURE 3 HERE).****Sensitivity analyses**

Subgroup analyses investigating the risk of BC of current smokers versus never smokers were performed to check for the influence of potential sources of heterogeneity (**Figure 2**). Most subgroup estimates seemed to be consistent with each other and did not indicate heterogeneity. However, the SOR of 1.91 (95% CI=1.65-2.17) for the 7 included Asian

studies was lower compared to both European ( $n=25$ ,  $p=3.93 \times 10^{-7}$ ) and North-American ( $n=34$ ,  $p=4.40 \times 10^{-6}$ ) estimates (). Of these 7 studies (including 2,760 cases), 4 investigated Chinese populations (84, 85, 93, 96), 2 investigated Japanese populations (18, 91) and there was one prospective study in a Korean population (69) to estimate the effect of smoking on BC risk. Across these 7 studies, estimates consistently indicated a two-fold increase of BC risk as opposed to the overall (and European and American) estimate of a three-fold increased risk of BC for current smokers compared to never smokers.

A cumulative meta-analysis, performed to check whether the risk estimate of BC for current smokers compared to never smokers changed over time since (included publications appeared in print between 1968 and 2015) indicated that there was a slight increase of BC risk for current smokers versus never smokers over time (**Supplemental Figure 1**). However, when only considering multiple adjusted (at least adjusted for age and sex) estimates, there were no changes in estimated risk of BC.

In addition to the presented dose-response curves estimated by GLS regression using restricted cubic splines, other methods (VWLS, linear regression) did not show different results compared to GLS with regard to the estimated regression slope for all investigated smoking characteristics. Furthermore, the shape of the dose-response curves did not change substantially by varying with positioning of knots using the cubic splines method or when applying a fractional polynomials approach for curve estimation.

### **Population attributable risks**

In Europe approximately 28% of males and 18% of females smoke (3), whereas in the USA these figures are estimated to be 21% and 16% (4). By combining these figures with the pooled risk estimates per continent from this meta-analysis PARs were calculated (**Table 3**). The fraction of BC cases attributable to cigarette smoking is 43% for males and 26% for

females in Europe and 34% for males and 30% for females in the USA. Unfortunately, no studies presenting gender-specific ORs were found for the Chinese population, however the PAR in the whole population seems smaller (20%) compared to both Europe and the USA, while the prevalence of smoking is larger in China (5). **(TABLE 3 HERE)**

## **CONCLUSIONS**

This meta-analysis summarizes the findings of 89 observational studies encompassing a total of 57 145 BC cases investigating the association between cigarette smoking and BC risk.

### **Smoking status and age at first exposure influence BC risk**

Our findings support earlier reviews in indicating an increased risk of BC for cigarette smokers. Age at first exposure is negatively associated with BC risk, however no studies adjusted for smoking duration or smoking intensity as possible effect modifiers in the included publications.

### **Dose-response relationship between smoking intensity and BC risk with a risk plateau at 15 cigarettes a day**

Increasing smoking intensity (i.e. smoking more cigarettes per day) seems to be of less additional impact on BC risk when smoking more than 15 cigarettes a day. Perhaps surprisingly, very heavy smokers (e.g. 50 cigarettes a day) do not experience a markedly increased risk compared to less heavy smokers. A similar relationship is observed for pack-years, but with a risk plateau at approximately 50 pack-years. These results are in line with experimental and molecular epidemiological studies in which saturation is observed of smoking-related DNA adduct levels in lymphocytes and lung cells at higher doses, leading to non-linear dose-response relationships (111). In the bladders of mice treated with the bladder carcinogen 4-aminobiphenyl (4-ABP), adduct levels in bladder-DNA and associated bladder tumours increased by dose at low doses, but saturation was observed at high doses (112). Similarly in smokers, adduct levels (derived from the tobacco carcinogens Polycyclic Aromatic Hydrocarbons and 4-ABP) in blood cells plateaued at 20 cigarettes per day (113), which is in agreement with the presently observed dose-response relationship in BC risk. Although these studies might provide some biological explanation for the observed risk

plateau it is not replicated in other smoking-related cancers such as lung cancer (114), where the association seems to be linear, or head-and neck cancer where some studies show a similar risk plateau (115) but others indicate a linear association (116). Therefore, more research is needed on the possible mechanism that underlies the observed association between smoking intensity and BC risk.

### **Smoking cessation is most beneficial more than 20 years prior to diagnosis, but still causes a long-term BC risk increase**

Many smokers believe that smoking cessation will cause their risk of several diseases to return to the risk of a non-smoker over a very short period (117). However, this analysis unambiguously shows that lowering BC risk after smoking cessation takes time. The beneficial effect of smoking cessation on BC risk is largest when having stopped smoking more than 20 years prior to diagnosis. Even then the risk of former smokers does not return to the risk of non-smokers. Even after 20 years of cessation, ex-smokers remain at a 50% increased risk compared to those who have never smoked. Furthermore, there does not seem to be a substantial risk reduction between 5 and 15 years of smoking cessation prior to diagnosis. Although smoking cessation seems to be the only efficient mechanism to counteract smoking-induced pathogenic processes leading to cancer (118), these results show that the malignant effects of exposure to tobacco-related carcinogens can linger for a lifetime in the bladder. The risk of BC per year of smoking increases gradually every year, indicating that smoking cessation programmes should aim to achieve smoking cessation as early in life as possible to effectively decrease BC risk due to smoking. The presented dose-response curves might be useful aids for developing such smoking cessation strategies.

### **Lower risk of BC for smokers in Asian compared to Caucasian populations**

All studies in Asian populations observed lower ORs compared to pooled estimates from Europe and the USA. A similar difference was observed in lung cancer, where a meta-analysis showed a markedly lower pooled RR for smokers compared to never-smokers in Asian populations (pooled RR=5.52, 95% CI=2.83-10.78) compared to studies in Caucasian populations (pooled RR=9.94, 95% CI=5.92, 16.67) (119). Even though the exact mechanism behind this lower susceptibility for tobacco-related cancers in Asian populations remains unclear, there is some evidence that nicotine intake from cigarette smoking is lower and that therefore Asian populations might be less susceptible to the harmful effects of tobacco smoke compared to Caucasian populations (120).

### **Decreased population attributable risk (PAR) in Western countries for cigarette smoking in BC**

The PAR calculated for Europe was noticeably lower compared to the estimated PAR from the 2000 meta-analysis (2), where it was estimated that 50% of male cases and 35% of female cases were attributable to smoking, as opposed to the 43% and 26% for men and women respectively which were estimated in the current meta-analysis. This indicates that the burden of smoking on bladder cancer incidence has decreased. Although we have no earlier PAR estimate for the USA, it is likely that a similar decrease in BC risk attributable to smoking has occurred during the past 15 years. These lower figures are due to the currently decreasing number of smokers in these populations (3, 4), since the risk of BC associated with smoking remains unaltered as we show in our cumulative meta-analysis. Even though the PARs were lower, the total number of worldwide incident BC cases only slightly decreased from 356 557 in 2002 (121) to 330 380 in 2012 (1), emphasizing the continuing importance of development of effective smoking cessation and prevention programmes. Interestingly, a pooled analysis from Nordic countries found very similar PARs (41% in males and 32% in females) to what we have observed now already in 1997 (122), indicating that there might be meaningful

differences in PAR even at a regional level. Unfortunately, no PAR has been calculated previously for Eastern countries so we could not compare our estimated PAR for China to previous results. However, since smoking prevalence is still on the rise in China (5), it is highly unlikely that the PAR has decreased over the past years in China or other Eastern countries.

### **Bias and heterogeneity**

Although the number of included studies was large, many articles did not present adjusted risk estimates. Since there was a difference in pooled OR between studies showing adjusted estimates compared to unadjusted estimates, we expect that not adjusting for at least age and sex might lead to underestimation of the strength of the association between smoking and BC incidence given the higher pooled OR for adjusted risk estimates. In the dose-response meta-analysis, both adjusted and unadjusted risk estimates were included and there was no heterogeneity between studies caused by the number of factors adjusted for.

In this meta-analysis, publication bias may have played a role since no attempts were made to include unpublished observations and several studies were excluded because of not meeting the selection criteria. Additionally, when investigating funnel plots, the observed bias was bipolar (e.g. included both higher and lower estimates) and occurred mostly between larger studies. Since some degree of heterogeneity was likely to occur due to differences in study methodology (e.g. study population, design, smoking assessment) between the large number of studies included, a random effects approach to the meta-analyses was used. This approach allowed for more heterogeneity in studies beyond sampling error, as opposed to a fixed effects approach (123).

### **Sensitivity analyses**

Subgroup analyses showed that SORs were similar across several possible sources of heterogeneity, except for studies from Asian populations. A cumulative meta-analysis showed no time effect on the overall risk estimate of smoking for BC. Although several regression methods were used for dose-response curve estimation, there were no differences between the shapes of the estimated curves resulting from the different analyses. Also, varying the knots (which determine how the curves are estimated) did not cause major changes in the shape of the curves. Both of these observations lead to the conclusion that the presented GLS curves are robust and can be interpreted as such.

### **Study limitations**

Because only 15 studies which adjusted for multiple factors (of which 8 adjusted their BC risk estimates for smokers for factors other than age and sex) were included, the pooled estimates obtained are not completely free of possible confounding due to other factors influencing BC risk. The number of studies adjusting for multiple risk factors was probably low because especially the more recently published studies often do not focus solely on smoking but only considered smoking status as a stratifying factor in their molecular analyses for example. Nevertheless, apart from smoking, only occupational exposure to carcinogens has been identified as a major risk factor for BC. Since the frequency of occupational exposure is so long it is unlikely to be a confounder and therefore many individual studies may have not corrected for this. In addition, studies included in this meta-analysis did not include sufficient data to stratify for important molecular aberrations which play a role in BC development. Studies on molecular determinants of BC development have unveiled *TP53* mutation and chromosome 9 defects as frequent molecular aberrations in BC aetiology (124, 125). Also, glutathione S-transferase M1 (GSTM1) and N-acetyl transferase2 (NAT2) deficiency are both associated with increased bladder cancer risk and are together estimated to account for about 30% of bladder cancer cases in Caucasian populations (126). Recently,

several single nucleotide polymorphisms (SNPs) associated with increased risk of BC have been identified on candidate genes such as fibroblast growth factor receptor 3 (FGFR3) and telomerase reverse transcriptase (TERT) (127). Some case-control studies focusing on molecular aberrations and BC also included data on smoking, however almost all of the molecular studies found in our search did not present any useable smoking data for this meta-analysis.

## **Conclusion**

Our findings are in line with results from earlier meta-analyses and reviews indicating an estimated threefold higher risk of BC for cigarette smokers. Age at first exposure was negatively associated with BC risk. The proportions of BC cases attributable to smoking (PARs) were noticeably lower than estimated in 2000 for both males and females, driven by the decreasing number of smokers in Western countries. Furthermore, we estimated dose-response curves providing a more graphic quantification of the impact of smoking intensity, pack-years, duration and cessation on BC risk which provide opportunities for development of smoking cessation- and prevention programmes which should aim for smoking cessation at an early age.

## References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E86.
2. Zeegers M, Tan FE, Dorant E, van den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk. *Cancer*. 2000;89(3):630-9.
3. OECD. Health at a Glance: Europe 2014. OECD Publishing [Internet]. 2014. Available from: [http://dx.doi.org/10.1787/health\\_glance\\_eur-2014-en](http://dx.doi.org/10.1787/health_glance_eur-2014-en).
4. Agaku IT, King BA, Dube SR, Control CfD, Prevention. Current cigarette smoking among adults—United States, 2005–2012. *MMWR Morb Mortal Wkly Rep*. 2014;63(2):29-34.
5. Li Q, Hsia J, Yang G. Prevalence of smoking in China in 2010. *NEJM*. 2011;364(25):2469-70.
6. Letašiová S, Medve’Ova A, Šovčíková A, Dušinská M, Volkovová K, Mosoiu C, et al. Bladder cancer, a review of the environmental risk factors. *Environ Health*. 2012;11(Suppl 1):S11.
7. Zeegers MP, Kellen E, Buntinx F, van den Brandt PA. The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. *World J Urol*. 2004;21(6):392-401.
8. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M, group CRAC. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*. 2005;366(9499):1784-93.
9. Wells G, Shea B, O’Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON—Ottawa Hospital Research Institute, 2013. 2014.
10. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-34.
11. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*. 2012;175(1):66-73.
12. Dunham LJ, Rabson AS, Stewart HL, Frank AS, Young JL. Rates, Interview, and Pathology Study of Cancer of the Urinary Bladder in New Orleans, Louisiana. *Journal of the National Cancer Institute*. 1968;41(3):683-709.
13. Anthony HM, Thomas GM. Bladder tumours and smoking. *Int J Cancer*. 1970;5(2):266-72.
14. Armstrong B, Garrod A, Doll R. A retrospective study of renal cancer with special reference to coffee and animal protein consumption. *Br J Cancer*. 1976;33(2):127-36.
15. Miller A, Howe G. Artificial sweeteners and bladder cancer. *Lancet*. 1977;310(8050):1221-2.
16. Wynder EL, Stellman SD. Comparative epidemiology of tobacco-related cancers. *Cancer Res*. 1977;37(12):4608-22.
17. Vineis P, Segnan N, Costa G, Terracini B. Evidence of a multiplicative effect between cigarette smoking and occupational exposures in the aetiology of bladder cancer. *Cancer Lett*. 1981;14(3):285-90.
18. Morrison AS, Buring JE, Verhoek WG, Aoki K, Leck I, Ohno Y, et al. An international study of smoking and bladder cancer. *J Urol*. 1984;131(4):650-4.

19. 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(3):455-61.
20. Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol*. 1985;121(1):37-48.
21. Vineis P, Ciccone G, Ghisetti V, Terracini B. Cigarette smoking and bladder cancer in females. *Cancer Lett*. 1985;26(1):61-6.
22. Wynder EL, Dieck GS, Hall NE, Lahti H. A case-control study of diesel exhaust exposure and bladder cancer. *Environ Res*. 1985;37(2):475-89.
23. 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. *Am J Epidemiol*. 1986;124(4):578-89.
24. Brownson RC, Chang JC, Davis JR. Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *Am J Public Health*. 1987;77(10):1298-300.
25. 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(6):1119-25.
26. Augustine A, Hebert JR, Kabat GC, Wynder EL. Bladder cancer in relation to cigarette smoking. *Cancer Res*. 1988;48(15):4405-8.
27. Slattery ML, Schumacher MC, West DW, Robison LM. Smoking and bladder cancer. The modifying effect of cigarettes on other factors. *Cancer*. 1988;61(2):402-8.
28. Steineck G, Norell SE, Feychting M. Diet, tobacco and urothelial cancer. A 14-year follow-up of 16,477 subjects. *Acta Oncol*. 1988;27(4):323-7.
29. Vineis P, Esteve J, Hartge P, Hoover R, Silverman DT, Terracini B. Effects of timing and type of tobacco in cigarette-induced bladder cancer. *Cancer Res*. 1988;48(13):3849-52.
30. Burch J, Rohan T, Howe G, Risch H, Hill G, Steele R, et al. Risk of bladder cancer by source and type of tobacco exposure: A case-control study. *Int J Cancer*. 1989;44(4):622-8.
31. Helzlsouer KJ, Comstock GW, Morris JS. Selenium, lycopene, alpha-tocopherol, beta-carotene, retinol, and subsequent bladder cancer. *Cancer Res*. 1989;49(21):6144-8.
32. Ross RK, Paganini-Hill A, Landolph J, Gerkins V, Henderson BE. Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter. *Cancer Res*. 1989;49(4):1045-8.
33. D'Avanzo B, Negri E, La Vecchia C, Gramenzi A, Bianchi C, Franceschi S, et al. Cigarette smoking and bladder cancer. *European journal of cancer (Oxford, England : 1990)*. 1990;26(6):714-8.
34. Harris RE, Chen-Backlund JY, Wynder EL. Cancer of the urinary bladder in blacks and whites. A case-control study. *Cancer*. 1990;66(12):2673-80.
35. Hartge P, Harvey EB, Linehan WM, Silverman DT, Sullivan JW, Hoover RN, et al. Unexplained excess risk of bladder cancer in men. *J Natl Cancer Inst*. 1990;82(20):1636-40.
36. 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(2):536-40.
37. La Vecchia C, Negri E, D'Avanzo B, Savoldelli R, Franceschi S. Genital and urinary tract diseases and bladder cancer. *Cancer Res*. 1991;51(2):629-31.
38. Lopez-Abente G, Gonzalez CA, Errezola M, Escolar A, Izarzugaza I, Nebot M, et al. Tobacco smoke inhalation pattern, tobacco type, and bladder cancer in Spain. *Am J Epidemiol*. 1991;134(8):830-9.
39. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. *Am J Epidemiol*. 1991;133(3):230-9.

40. D'Avanzo B, La Vecchia C, Franceschi S, Negri E, Talamini R, Buttino I. Coffee consumption and bladder cancer risk. *European journal of cancer (Oxford, England : 1990)*. 1992;28A(8-9):1480-4.
41. Kunze E, Chang-Claude J, Frentzel-Beyrne R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer*. 1992;69(7):1776-90.
42. McLaughlin JK, Silverman DT, Hsing AW, Ross RK, Schoenberg JB, Yu MC, et al. Cigarette smoking and cancers of the renal pelvis and ureter. *Cancer Res*. 1992;52(2):254-7.
43. Chyou P-H, Nomura AMY, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol*. 1993;3(3):211-6.
44. Cordier S, Clavel J, Limasset JC, Boccon-Gibod L, Le Moual N, Mandereau L, et al. Occupational risks of bladder cancer in France: a multicentre case-control study. *Int J Epidemiol*. 1993;22(3):403-11.
45. Hayes RB, Friedell GH, Zahm SH, Cole P. Are the known bladder cancer risk-factors associated with more advanced bladder cancer? *Cancer causes & control : CCC*. 1993;4(2):157-62.
46. Barbone F, Franceschi S, Talamini R, Bidoli E, La Vecchia C. Occupation and bladder cancer in Pordenone (north-east Italy): a case-control study. *Int J Epidemiol*. 1994;23(1):58-65.
47. Sorahan T, Lancashire RJ, Sole G. Urothelial cancer and cigarette smoking: findings from a regional case-controlled study. *Br J Urol*. 1994;74(6):753-6.
48. Sturgeon SR, Hartge P, Silverman DT, Kantor AF, Linehan WM, Lynch C, et al. Associations between bladder cancer risk factors and tumor stage and grade at diagnosis. *Epidemiology*. 1994;5(2):218-25.
49. D'Avanzo B, La Vecchia C, Negri E, Decarli A, Benichou J. Attributable risks for bladder cancer in northern Italy. *Ann Epidemiol*. 1995;5(6):427-31.
50. Tremblay C, Armstrong B, Theriault G, Brodeur J. Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. *Am J Ind Med*. 1995;27(3):335-48.
51. Bruemmer B, White E, Vaughan TL, Cheney CL. Nutrient intake in relation to bladder cancer among middle-aged men and women. *Am J Epidemiol*. 1996;144(5):485-95.
52. Engeland A, Andersen A, Haldorsen T, Tretli S. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. *Cancer causes & control : CCC*. 1996;7(5):497-506.
53. Bedwani R, el-Khwsy F, Renganathan E, Braga C, Abu Seif HH, Abul Azm T, et al. Epidemiology of bladder cancer in Alexandria, Egypt: tobacco smoking. *International journal of cancer Journal international du cancer*. 1997;73(1):64-7.
54. Donato F, Boffetta P, Fazioli R, Aulenti V, Gelatti U, Porru S. Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, northern Italy. *Eur J Epidemiol*. 1997;13(7):795-800.
55. Teschke K, Morgan MS, Checkoway H, Franklin G, Spinelli JJ, van Belle G, et al. Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens. *Occup Environ Med*. 1997;54(6):443-51.
56. Koivusalo M, Hakulinen T, Vartiainen T, Pukkala E, Jaakkola JJ, Tuomisto J. Drinking water mutagenicity and urinary tract cancers: a population-based case-control study in Finland. *Am J Epidemiol*. 1998;148(7):704-12.
57. Sorahan T, Hamilton L, Wallace DM, Bathers S, Gardiner K, Harrington JM. Occupational urothelial tumours: a regional case-control study. *Br J Urol*. 1998;82(1):25-32.
58. Pohlabein H, Jockel KH, Bolm-Audorff U. Non-occupational risk factors for cancer of the lower urinary tract in Germany. *Eur J Epidemiol*. 1999;15(5):411-9.

59. Pommer W, Bronder E, Klimpel A, Helmert U, Greiser E, Molzahn M. Urothelial cancer at different tumour sites: role of smoking and habitual intake of analgesics and laxatives. Results of the Berlin Urothelial Cancer Study. *Nephrol Dial Transplant*. 1999;14(12):2892-7.
60. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W. Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter Urothelial and Renal Cancer. *Int J Epidemiol*. 2000;29(2):238-47.
61. Serra C, Bonfill X, Sunyer J, Urrutia G, Turuguet D, Bastus R, et al. Bladder cancer in the textile industry. *Scand J Work Environ Health*. 2000;26(6):476-81.
62. Castelao JE, Yuan J-M, Skipper PL, Tannenbaum SR, Gago-Dominguez M, Crowder JS, et al. Gender-and smoking-related bladder cancer risk. *Journal of the National Cancer Institute*. 2001;93(7):538-45.
63. Chiu BC, Lynch CF, Cerhan JR, Cantor KP. Cigarette smoking and risk of bladder, pancreas, kidney, and colorectal cancers in Iowa. *Ann Epidemiol*. 2001;11(1):28-37.
64. Vineis P, Marinelli D, Autrup H, Brockmoller J, Cascorbi I, Daly AK, et al. Current Smoking, Occupation, N-Acetyltransferase-2 and Bladder Cancer A Pooled Analysis of Genotype-based Studies. *Cancer Epidemiol Biomarkers Prev*. 2001;10(12):1249-52.
65. Pelucchi C, La Vecchia C, Negri E, Dal Maso L, Franceschi S. Smoking and other risk factors for bladder cancer in women. *Prev Med*. 2002;35(2):114-20.
66. Tripathi A, Folsom AR, Anderson KE. Risk factors for urinary bladder carcinoma in postmenopausal women. The Iowa Women's Health Study. *Cancer*. 2002;95(11):2316-23.
67. Zeegers MP, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control*. 2002;13(1):83-90.
68. Gaertner RR, Trpeski L, Johnson KC. A case-control study of occupational risk factors for bladder cancer in Canada. *Cancer Causes Control*. 2004;15(10):1007-19.
69. Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS. Smoking and cancer risk in Korean men and women. *Cancer Causes Control*. 2004;15(4):341-8.
70. Karagas MR, Tosteson TD, Morris JS, Demidenko E, Mott LA, Heaney J, et al. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. *Cancer Causes Control*. 2004;15(5):465-72.
71. Quirk JT, Li Q, Natarajan N, Mettlin CJ, Cummings KM. Cigarette smoking and the risk of bladder cancer in men and women. *Tob Induc Dis*. 2004;2(3):1-4.
72. Cao W, Cai L, Rao JY, Pantuck A, Lu ML, Dalbagni G, et al. Tobacco smoking, GSTP1 polymorphism, and bladder carcinoma. *Cancer*. 2005;104(11):2400-8.
73. Chen Y-C, Su H-JJ, Guo Y-LL, Houseman EA, Christiani DC. Interaction between environmental tobacco smoke and arsenic methylation ability on the risk of bladder cancer. *Cancer Causes Control*. 2005;16(2):75-81.
74. Bjerregaard BK, Raaschou-Nielsen O, Sørensen M, Frederiksen K, Christensen J, Tjønneland A, et al. Tobacco smoke and bladder cancer—in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2006;119(10):2412-6.
75. Cantwell MM, Lacey JV, Schairer C, Schatzkin A, Michaud DS. Reproductive factors, exogenous hormone use and bladder cancer risk in a prospective study. *Int J Cancer*. 2006;119(10):2398-401.
76. Samanic C, Kogevinas M, Dosemeci M, Malats N, Real FX, Garcia-Closas M, et al. Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev*. 2006;15(7):1348-54.
77. Terry PD, Umbach DM, Taylor JA. APE1 genotype and risk of bladder cancer: evidence for effect modification by smoking. *Int J Cancer*. 2006;118(12):3170-3.

78. Alberg AJ, Kouzis A, Genkinger JM, Gallicchio L, Burke AE, Hoffman SC, et al. A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol.* 2007;165(6):660-6.
79. Jiang X, Yuan J-M, Skipper PL, Tannenbaum SR, Mimi CY. Environmental tobacco smoke and bladder cancer risk in never smokers of Los Angeles County. *Cancer Res.* 2007;67(15):7540-5.
80. McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I. Telomere length, cigarette smoking, and bladder cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2007;16(4):815-9.
81. Demirel F, Cakan M, Yalçinkaya F, Topcuoglu M, Altug U. The association between personal habits and bladder cancer in Turkey. *Int Urol Nephrol.* 2008;40(3):643-7.
82. Baris D, Karagas MR, Verrill C, Johnson A, Andrew AS, Marsit CJ, et al. A case-control study of smoking and bladder cancer risk: emergent patterns over time. *Journal of the National Cancer Institute.* 2009;101(22):1553-61.
83. Cassidy A, Wang W, Wu X, Lin J. Risk of urinary bladder cancer: a case-control analysis of industry and occupation. *BMC Can.* 2009;9(1):443.
84. Stern MC, Van Den Berg D, Yuan J-M, Conti DV, Gago-Dominguez M, Pike MC, et al. Sequence variant on 3q28 and urinary bladder cancer risk: findings from the los angeles-shanghai bladder case-control study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(11):3057-61.
85. Wen H, Ding Q, Fang Z-j, Xia G-w, Fang J. Population study of genetic polymorphisms and superficial bladder cancer risk in Han-Chinese smokers in Shanghai. *Int Urol Nephrol.* 2009;41(4):855-64.
86. Srivastava P, Gangwar R, Kapoor R, Mittal RD. Bladder cancer risk associated with genotypic polymorphism of the matrix metalloproteinase-1 and 7 in North Indian population. *Dis Markers.* 2010;29(1):37-46.
87. Tao L, Xiang Y-B, Wang R, Nelson HH, Gao Y-T, Chan KK, et al. Environmental tobacco smoke in relation to bladder cancer risk—the Shanghai bladder cancer study. *Cancer Epidemiol Biomarkers Prev.* 2010;19(12):3087-95.
88. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA.* 2011;306(7):737.
89. Gangwar R, Mandhani A, Mittal RD. Functional polymorphisms of cyclooxygenase-2 (COX-2) gene and risk for urinary bladder cancer in North India. *Surgery.* 2011;149(1):126-34.
90. MacKenzie T, Zens MS, Ferrara A, Schned A, Karagas MR. Diabetes and risk of bladder cancer: evidence from a case-control study in New England. *Cancer.* 2011;117(7):1552-6.
91. Grant EJ, Ozasa K, Preston D, Suyama A, Shimizu Y, Sakata R, et al. Effects of radiation and lifestyle factors on risks of urothelial carcinoma in the life span study of atomic bomb survivors. *Radiat Res.* 2012;178(1):86-98.
92. Jiang X, Castelao JE, Yuan JM, Stern MC, Conti DV, Cortessis VK, et al. Cigarette smoking and subtypes of bladder cancer. *Int J Cancer.* 2012;130(4):896-901.
93. Liu Y, Wang H, Lin T, Wei Q, Zhi Y, Yuan F, et al. Interactions between cigarette smoking and XPC-PAT genetic polymorphism enhance bladder cancer risk. *Oncol Rep.* 2012;28(1):337-45.
94. Welty CJ, Wright JL, Hotaling JM, Bhatti P, Porter MP, White E, editors. Persistence of urothelial carcinoma of the bladder risk among former smokers: Results from a contemporary, prospective cohort study. *Urologic Oncology: Seminars and Original Investigations*; 2012: Elsevier; 2012.

95. Ferreccio C, Yuan Y, Calle J, Benítez H, Parra RL, Acevedo J, et al. Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer. *Epidemiology*. 2013;24(6):898-905.
96. Isa F, Xie L-P, Hu Z, Zhong Z, Hemelt M, Reulen RC, et al. Dietary consumption and diet diversity and risk of developing bladder cancer: results from the South and East China case-control study. *Cancer Causes Control*. 2013;24(5):885-95.
97. Matic M, Pekmezovic T, Djukic T, Mimic-Oka J, Dragicevic D, Krivic B, et al., editors. *GSTA1, GSTM1, GSTP1, and GSTT1 polymorphisms and susceptibility to smoking-related bladder cancer: A case-control study*. *Urologic Oncology: Seminars and Original Investigations*; 2013: Elsevier.
98. Amr S, Dawson R, Saleh DaA, Magder LS, Mikhail NN, St. George DM, et al. Agricultural workers and urinary bladder cancer risk in Egypt. *Arch Environ Health*. 2014;69(1):3-10.
99. Polesel J, Bosetti C, di Maso M, Montella M, Libra M, Garbeglio A, et al. Duration and intensity of tobacco smoking and the risk of papillary and non-papillary transitional cell carcinoma of the bladder. *Cancer Causes Control*. 2014;25(9):1151-8.
100. Vermeulen S, Hanum N, Grotenhuis A, Castaño-Vinyals G, van der Heijden A, Aben K, et al. Recurrent urinary tract infection and risk of bladder cancer in the Nijmegen bladder cancer study. *Br J Cancer*. 2014.
101. Baena AV, Allam MF, Del Castillo AS, Díaz-Molina C, Tapia MJR, Abdel-Rahman AG, et al. Urinary bladder cancer risk factors in men: a Spanish case-control study. *Eur J Cancer Prev*. 2006;15(6):498-503.
102. Sadetzki S, Bensal D, Blumstein T, Novikov I, Modan B. Selected risk factors for transitional cell bladder cancer. *Med Oncol*. 2000;17(3):179-82.
103. Hours M, Dananche B, Fevotte J, Bergeret A, Ayzac L, Cardis E, et al. Bladder cancer and occupational exposures. *Scand J Work Environ Health*. 1994:322-30.
104. Jiang X, Castela JE, Groshen S, Cortessis VK, Ross RK, Conti DV, et al. Alcohol consumption and risk of bladder cancer in Los Angeles County. *Int J Cancer*. 2007;121(4):839-45.
105. Hartge P, Hoover R, Kantor A. Bladder cancer risk and pipes, cigars, and smokeless tobacco. *Cancer*. 1985;55(4):901-6.
106. Vineis P, Frea B, Uberti E, Ghisetti V, Terracini B. Bladder cancer and cigarette smoking in males: a case-control study. *Tumori*. 1983;69(1):17-22.
107. Jensen OM, Wahrendorf J, Blettner M, Knudsen J, Sørensen B. The Copenhagen case-control study of bladder cancer: role of smoking in invasive and non-invasive bladder tumours. *J Epidemiol Community Health*. 1987;41(1):30-6.
108. Lin J, Spitz MR, Dinney CP, Etzel CJ, Grossman HB, Wu X. Bladder cancer risk as modified by family history and smoking. *Cancer*. 2006;107(4):705-11.
109. Wang Y-H, Yeh S-D, Wu M-M, Liu C-T, Shen C-H, Shen K-H, et al. Comparing the joint effect of arsenic exposure, cigarette smoking and risk genotypes of vascular endothelial growth factor on upper urinary tract urothelial carcinoma and bladder cancer. *J Hazard Mater*. 2013;262:1139-46.
110. McCormack VA, Agudo A, Dahm CC, Overvad K, Olsen A, Tjønneland A, et al. Cigar and pipe smoking and cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2010;127(10):2402-11.
111. Godschalk RW, Van Schooten F-J, Bartsch H. A critical evaluation of DNA adducts as biological markers for human exposure to polycyclic aromatic compounds. *Biochem Mol Biol Int*. 2003;36(1):1-11.

112. Poirier MC, Fullerton NF, Smith BA, Beland FA. DNA adduct formation and tumorigenesis in mice during the chronic administration of 4-aminobiphenyl at multiple dose levels. *Carcinogenesis*. 1995;16(12):2917-21.
113. Dallinga JW, Pachen D, Wijnhoven S, Breedijk A, van't Veer L, Wigbout G, et al. The use of 4-aminobiphenyl hemoglobin adducts and aromatic DNA adducts in lymphocytes of smokers as biomarkers of exposure. *Cancer Epidemiol Biomarkers Prev*. 1998;7(7):571-7.
114. Lee PN, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Can*. 2012;12(1):385.
115. Wyss A, Hashibe M, Chuang S-C, Lee Y-CA, Zhang Z-F, Yu G-P, et al. Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Am J Epidemiol*. 2013;178(5):679-90.
116. Maasland DH, van den Brandt PA, Kremer B, Goldbohm RAS, Schouten LJ. Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. *BMC Can*. 2014;14(1):187.
117. De Vries H, Mudde AN, Dijkstra A, Willemsen MC. Differential beliefs, perceived social influences, and self-efficacy expectations among smokers in various motivational phases. *Prev Med*. 1998;27(5):681-9.
118. Department of Health and Human Services US. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general: Centers for Disease Control and Prevention (US); 2010.
119. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: A meta-analysis. *Int J Cancer*. 2008;122(1):155-64.
120. Benowitz NL, Pérez-Stable EJ, Herrera B, Jacob P. Slower metabolism and reduced intake of nicotine from cigarette smoking in Chinese-Americans. *Journal of the National Cancer Institute*. 2002;94(2):108-15.
121. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer*. 2005;55(2):74-108.
122. Dreyer L, Winther J, Pukkala E, Andersen A. Tobacco smoking. *Apmis*. 1997;105(S76):9-47.
123. Hedges LV, Vevea JL. Fixed-and random-effects models in meta-analysis. *Psychol Methods*. 1998;3(4):486.
124. Hartmann A, Schlake G, Zaak D, Hungerhuber E, Hofstetter A, Hofstaedter F, et al. Occurrence of chromosome 9 and p53 alterations in multifocal dysplasia and carcinoma in situ of human urinary bladder. *Cancer Res*. 2002;62(3):809-18.
125. Spruck CH, Rideout WM, Olumi AF, Ohneseit PF, Yang AS, Tsai YC, et al. Distinct pattern of p53 mutations in bladder cancer: relationship to tobacco usage. *Cancer Res*. 1993;53(5):1162-6.
126. García-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M, Hein DW, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet*. 2005;366(9486):649-59.
127. Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. *Nat Rev Cancer*. 2015;15(1):25-41.

## List of Tables and Figures

**Table 1. Study characteristics of included epidemiologic studies with data on cigarette smoking and urothelial cell carcinoma, ordered by year of publication**

**Table 2. Unadjusted and adjusted summary odds ratios for smoking status, age at first exposure**

**Table 3. Population attributable risk (PAR) of bladder cancer according to exposure to cigarette smoking in North-America, Europe and China**

**Figure 1. Flowchart of study selection and exclusion criteria**

**Figure 2. Forest plot depicting crude summary odds ratios (SOR) for current smokers versus non-smokers, by several possible sources of heterogeneity. The dashed line represents no effect and the solid line stands for the overall crude SOR of 2.96.**

**Figure 3. Dose-response curves with estimated ORs for smoking intensity (a), pack-years (b), duration (c) and years of smoking cessation (d). ORs are listed on the y-axis and units of smoking are given on the x-axis. Never smokers are the reference category for all calculated ORs.**

**Supplemental Figure 1. Cumulative meta-analysis results including OR from all studies comparing BC risk between current smokers and non-smokers. The dashed line represents the overall cumulative OR of 2.96 and the solid line stands for no effect.**