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

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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-Ottowa 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(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 ≤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^{th}, 35^{th}, 65^{th} and 95^{th} 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, $p=3.93*10^{-7}$) and North-American (n=34, $p=4.40*10^{-6}$) 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.

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