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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 107 fulfilled our inclusion criteria, of which 83 studies investigated BC and 24 investigated RCC. The pooled relative risk (RR) of BC incidence was 2.58 (95% confidence interval [CI] 2.37–2.80) for all smokers, 3.47 (3.07–3.91) for current smokers, and 2.04 (1.85–2.25) for former smokers. The corresponding pooled RR of BC disease-specific mortality (DSM) was 1.47 (1.24–1.75), 1.53 (1.12–2.09) and 1.44 (0.99–2.11). The pooled RR of RCC incidence was 1.31 (1.22–1.40) for all smokers, 1.36 (1.19–1.56) for current smokers, and 1.16 (1.08–1.25) for former smokers. The corresponding RCC DSM risk was 1.23 (1.08–1.40), 1.37 (1.19–1.59), and 1.02 (0.90–1.15).
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.

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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 second-hand 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. When results of a study were published in a single paper but also within a pooled analysis, we chose to include only the original study. 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