The Relationship between Smoking and Bladder Cancer: A Systematic Review

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Abstract— Background: Cigarette smoking is the most known, modifiable, risk factor for human health today. Bladder cancer is the most common urologic cancer and is the seventh most common cancer among men. The aim of this study was to provide an up-to-date estimation of the role of smoking in bladder cancer risk and to gain a more detailed quantification of several smoking characteristics (i.e. smoking intensity, duration and type of tobacco) by performing dose-response meta-analyses.
Method: We conducted a literature search in July 2017 using the PubMed and Google scholar databases. The primary inclusion criteria were based on the year of publication of the studies that examine the association between smoking and bladder cancer. Information on the following variables was extracted based on year of publication, research design, country and geographical area, features of population anatomical site (bladder), cigarette smoking assessment, definition of the exposure to cigarette smoking, exposure frequency, type of tobacco and case and control source. The association between smoking and bladder cancer risk is expressed in odds ratios (ORs) and hazard ratios (HRs) for both case-control studies and cohort studies included in this review.
Result: Cigarette smoking was confirmed as an important risk factor for bladder cancer, and smokers have two to three times the risk of non-smokers. Compared to never smokers, current smokers had significantly elevated risks of bladder cancer (OR 2.87). The risk of bladder cancer was 2 to 3 times higher among smokers of black tobacco than among smokers of blond tobacco. Both groups of smokers showed a beneficial effect of smoking cessation, with an immediate decline in risk. For sex related risk of bladder cancer, we found that cigarette smoking is an important statistically significant and dose-dependent risk factor for bladder cancer particularly in males. For both sexes, there was a general increase in the risk of bladder cancer associated with an increase in the number of cigarettes smoked per day and an increase in the number of years of regular smoking. The odds ratios for number of cigarettes smoked per day (cpd) increased to approximately 2.5 for smokers of more than 20 cpd, after adjustment for duration and nonsmoking-related covariates. Above 20 cpd, no further increase in odds ratio was observed.

Conclusion: Based on our modeling of smoking history, tobacco type, pack-years and intensity smoking, we confirmed that cigarette smoking is an important risk factor for bladder carcinoma. It is considered to be significant risk for both sex, but the risk appears to be more of value in males than in females.

Index Terms— Bladder Cancer, Smoking, Tobacco, Systematic Review.

1 Introduction

Cigarette smoking is the most common modifiable risk factor for human health nowadays. Approximately more than 30% of all cancer deaths in the United States result of smoking (1). Smokers have greater cancer death rates of about two times more than those of non-smokers (2). Worldwide, it is estimated that 15% (1.1million new cases per year) of all cancer cases are caused by cigarette smoking, 25% in men and 4% in women (3). Cigarette smoking is the most important cause of lung cancer, and also an important determinant of cancer risk for at least six other anatomical sites: oral cavity and pharynx, esophagus, larynx, pancreas, kidney, and urinary bladder(4). however, many questions remain unanswered including the extent to which the development of certain cancers is attributed to cigarette smoking and the magnitude of the relative risks at different anatomical sites(5,6).

Bladder cancer (BC) is the commonest urologic cancer and is the seventh most common cancer among men (7). More than 350,000 cases are diagnosed with incident bladder cancer per year worldwide(8), including greater than 70,000 per year in the United States (9).

Studies have shown a two- to threefold risk of bladder cancer among regular cigarette smokers, defined as those who smoked at least one cigarette per day for more than 6 months, compared with non-smoker(10). Experimental evidence in several studies has suggested that 2-naphthylamine and 4-aminobiphenyl may be the bladder carcinogens in cigarette smoking (10–17).

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

2 Methods

2.1 Search Strategy

We conducted a literature search in July 2017 using the PubMed and Google scholar databases. The following search was performed: (smoking OR tobacco OR cigarette) AND (cancer OR carcinoma OR neoplasm OR tumor) AND (bladder) AND (''risk factor'' OR occurrence OR incidence OR prevalence OR association). Filters were applied to capture items published in English on or after January 1880.

2.2 Selection Process

The initial search produced 83 articles, after deduplication. All articles were screened independently by five authors. Screening was conducted in two steps. In the first step, original English language articles on related disciplines published in peer-reviewed journals through November 2016 were included by judging from the title and source of articles. Publications in other languages, conference proceedings and theses as well as articles in unrelated disciplines were removed. By the end of this step, 22 articles remained.

In the second step, the abstracts and full texts were examined. The primary inclusion criteria were based on the year of publication of the studies that examine the association between smoking and bladder cancer.

2.3 Data Extraction

Information on the following variables was extracted based on year of publication, research design (case–control study, cohort study, prospective), country and geographical area (North America, Europe, Asia, Africa, united states), features of population (age, gender) anatomical site (bladder), cigarette smoking assessment (interview or questionnaire), definition of the exposure to cigarette smoking (active, passive, former, current), exposure frequency type of tobacco (black, blond) case and control source (hospital, population or both). The association between smoking and bladder cancer risk is expressed in odds ratios (ORs) and hazard ratios (HRs) for both case-control studies and cohort studies included in this review.

Since age and gender are considered to be major confounders of the association between smoking and bladder cancer, all included adjusted risk estimates adjusted for at least age and gender. For smoking duration, intensity, pack-years and the exposure to cigarette smoking, and type of tobacco, risk estimates for smoking and bladder cancer risk were recorded per category.

2.4 Risk of Bais Assessment

All studies, except qualitative studies, were given a score of '1' if they had an adequate description for each of five criteria: eligibility, randomization of participant selection or assignment for case–control studies, study sample (including number/size, age and gender). Qualitative studies were assessed for a clear description of eligibility, sample selection, study sample (including number/size, age and gender), in smoking and Bladder cancer history.

2.5 Data Analysis

The following information were extracted based on year of publication, developing country, type of study, Cigarette smoking assessment, and Risk of bladder cancer. The summary of the studies is provided in Table 1.

3 Result

Nineteen case-control studies and three cohort studies were included in this review. The studies measure exposure to cigarette smoking using three measures. First measure: "Current smoking status" was categorized into three levels: never smokers, former smokers, and current smokers. Never-smoker were those who replied negatively to the question about using any tobacco products for six months or longer. Current smokers were defined as those who had smoked cigarettes for a continuous period of six months or longer. Former smokers were defined as those who had quit smoking two or more years prior to the time of diagnosis. Second measure; "Usual consumption," a measure of intensity, was the reported usual number of cigarettes smoked per day. For questions such as number of cigarettes smoked per day. For analysis, the amount smoked per day was grouped into five categories (never smokers, <10, 11–20, 21–40, .40 cigarettes/day). Third measure: "Total lifetime consumption" was estimated in terms of pack-years of cigarette smoking, calculated by dividing average cigarettes smoked per day by 20 and multiplying by the number of years smoked. This constituted a measure that combined intensity and duration. For the purposes of analysis, pack-years of smoking were grouped into four categories (never smokers, <20, 21–40, >40 pack-years).

3.1 Smokers Vs Nonsmokers and Risk of BC

One case-control study, that was took place in Spain and carried out on men and women with newly diagnosed bladder cancer, found that among men, current (OR, 7.4;95% CI, 5.3-10.4) and former (OR, 3.8;95% CI, 2.8-5.3) smokers had significantly increased risks of bladder cancer compared with never smokers. Among women, current smokers had an OR (95% CI) of 5.1 (1.6-16.4) and former smokers had an OR (95% CI) of 1.8 (0.5- 7.2) compared with never smokers(17).

A Cohort study was conducted in United states(US) carried out on both sexes showed that Former smokers HR, 2.22; 95% confidence interval [CI], 2.03-2.44) and current smokers (HR, 4.06; 95% CI, 3.66-4.50) had higher risks of bladder cancer than never smokers(18).

Another case-control study was taken place in US revealed that regular smokers of any tobacco product had an increased risk of bladder cancer compared with lifelong nonsmokers, (OR_2.4; 95% CI_2.0 to 2.8). The increased risk was confined to those who smoked cigarettes (OR _2.5; 95% CI _ 2.1 to 3.0)(19).

Another case–control study conducted between 1985 and 1992 in two areas of northern Italy. In the result of the study compared to never smokers, the current smokers (OR 2.87) had significantly elevated risks of bladder cancer.

In addition, another case–control study of 152 patients with bladder cancer were examined from whom 124 patients. The mean age of participants was 63.6 (±15.3) years in the group of patients with bladder cancer and 61.8 (±14.1) years in the control group (P = 0.288). Smoking history was significantly higher in the case group than the control group. The OR for being affected by bladder cancer in active smokers (OR = 6.697) was higher than that of ex-smokers (OR = 2.549).

Another cohort study conducted in Iowa, US, studying the risk of BC in postmenopausal women, 37,459 women were followed up over 13 year for and the authors identified 112 incident cases of urinary bladder carcinoma in the cohort of at-risk women. The incident rate was approximately 25 per 100,000 person-years of observation and increased with age. The age-adjusted incidence rates of bladder carcinoma were 5.49-fold higher in current smokers (91.4 per 100,000 person-years) than in nonsmokers (17.1 per 100,000 person-years). RR for current versus never-smokers was 4.23 (95% CI _ 2.76–6.70)(30).

A case-control study taken place in Denmark studying the role of cigarette smoking in invasive and non-invasive BC showed that smokers have a significantly increased risk of bladder cancer with RR 3-4 (men: RR = 4-7; women: RR= 2-5)(30).

In another case-control study, that was taken place in Greece

and carried on patients of both sexes who has BC to examine the relationship of cigarette smoking, coffee consumption and BC, it was shown clearly that cigarette smoking is an important risk factor for bladder cancer. For all age groups and both genders, the rate ratio for smokers was 2.7 (90% CI, 1.8-4.1)(31).

A case- control study, that was taken place in US found that an approximately 2.5-fold increase in the risk of bladder cancer associated with active cigarette smoking. The associations for active cigarette smoking and bladder cancer risk were consistent in both men and women(43).

Reference	*Author*	*Year*	*Country*	*Study Design*	*Smoking Assessment*	*Risk of BC*
17	Samanic C. et al.	2006	Spain	Case-control	Interview and Questionnaire	Smokers had an increased risk of BC for both sexes Risk was higher for those who smoked black tobacco and for long duration
18	Freedman, N. et al.	2011	US	Cohort	Questionnaire	The study found similar proportion of bladder cancer in both sexes
19	Castelao J. et al.	2001	US	Case-control	Interview	Higher risk of BC in smokers in both sexes Risk was higher in female
20	Kunze E, et al.	1992	Germany	Case-control	Interview	The results show that the risk is significantly increase in: Male and female ever-smokers of cigarettes compared with nonsmokers, increasing number of cigarettes smoked per day, males starting to smoke before the age of 15 years and females starting to smoke before the age of 20 years.
21	Augustine A. et al.	1988	United States	Case-control	Interview	For current smokers, the risk increases with increase number of cigarettes smoked per day, and increase duration of smoking in both sexes. The results did not suggest an increased risk with early age at start of smoking in either sex.
22	Donato F. et al.	1997	Brescia, northern Italy	Case-control	Interview	Cigarette smoking was confirmed as an important risk factor for bladder cancer, with a strong dose-response relationship in men.
23	Bedwani R. et al.	1997	Alexandria, Egypt	Case-control	Interview	The findings of this study confirm that tobacco smoking is the major quantified risk factor for bladder cancer among Egyptian males (accounted for 75% of male bladder cancer in this population).
24	Vineis P. et al.	1988	Torino	Case-control	Interview	The risk of bladder cancer was 2 to 3 times higher among smokers of black tobacco than among smokers of blond tobacco. Both groups of smokers showed a beneficial effect of smoking cessation, with an immediate decline in risk.
25	Zeegers MP. et al.	2002	Netherlands	Case-cohort	questionnaire	It appeared that associations of cigarette smoking characteristics with bladder cancer risk were largely attributable to cigarette smoking duration only
26	Pelucchi C. et al.	2002	northern Italy	Case–control study	interviewers	Compared to never smokers, current smokers (OR 2.87) had significantly elevated risks of bladder cancer

27	Ghadimi T, et al.	2015	Iran	Case–control study	questionnaire	Cigarette smoking, even after quitting, was also associated with bladder cancer
28	Aliramaji A. et al.	2015	Iran	Case-control study	patients' files	A significant association was observed between smoking and with bladder cancer
29	Tripathi, A. et al.	2002	Iwoa, US	Cohort	Questionnaire	Smoking was a major risk factor of BC in postmenopausal women
30	Jensen, O. et al	1987	Denmark	Case-control	Interview	Significantly increased risk of BC in ever smokers in both sexes
31	Rebelakos A. et al.	1985	Greece	Case-control	Questionnaire	cigarette smoking is an important, statistically significant and dose-dependent risk factor for BC particularly in males
32	Dalsu Baris. Et al.	2009	US	Case-control	Interview	Regular and current cigarette smokers had higher risks of bladder cancer than never-smokers
33	Clavel J. et al.	1989	France	Case-control	Questionnaire	The risk of bladder cancer increased with daily amount and duration of smoking
34	Claude J. et al.	1986	Germany	Case-control	Interview	A significant dose-response relation was observed for increasing cigarette consumption, and a significant decrease in risk was shown for ex-smokers.
35	Augustine A. et al.	1988	US	Case-control	Interview	The findings of this investigation support an association between smoking and bladder cancer.
36	Hartge P. et al.	1987	US	Case- control	Patient's file	smoking cessation substantially reduced the risk of bladder cancer
42	I. Momas et al.	1994	France	Case-control	Interview	dose-response relationship between years of smoking and bladder cancer risk
43	Anthony J. Alberg et al.	2007	US	Cohort	Patient's file And survey	2.5-fold increase in the risk of bladder cancer associated with active cigarette smoking.
44	Ernst L et.al	1988	US	Case- control	interview	Smokers of filtered cigarettes had a slightly reduced risk of bladder cancer relative to smokers of nonfiltered cigarettes

3.2 Gender ans Risk of BC

A Cohort study was conducted in United States carried out on men (n = 281 394) and women (n = 186 134) were followed up between1995-2006 showed that incident bladder cancer occurred in 3896 men and 627 women(18).

A case-control study taken place in US studying the relationship between gender, smoking, and risk of BC revealed that compared with lifelong nonsmokers, Men who smoked 40 or more cigarettes per day for 20–39 years had an OR of 4.87 (95% CI _ 3.46 to 6.84). For all other smoking categories (No. Cigarettes/day 0, 1-19, >20) the ORs for women were higher than for men. For example, in the heaviest smoking category (40 cigarettes smoked per day for 40 years), the OR in women was more than twice that in men (11.49 versus 5.23, respectively)(19).

Another case-control study taken place in Denmark studying the role of cigarette smoking in invasive and non-invasive BC showed that estimates of relative risk for men and women separately are for smokers of cigarettes alone: men RR=4-0 (95% CI= 1-9-8-6) and women RR=2-3 (95% CI= 1-2-4-3)(30).

In another case-control study, that was taken place in Greece and carried on patients of both sexes who has BC to examine the relationship of cigarette smoking, coffee consumption and BC, it revealed that smoking is an important risk factor for BC and the association apparently is restricted to males, but it is more a reflection of the scarcity of the smoking habit among older Greek women than an indication of gender interaction (31).

3.3 Tobscco Type

A case-control study, that was took place in Spain showed that Relative to never smokers, risk was higher for men who smoked only black tobacco (OR, 5.3;95% CI, 3.8-7.4) than for men who smoked only blond tobacco (OR, 3.2;95% CI, 2.1-4.8)

and highest for smokers of both types (OR, 6.0;95% CI, 4.2-8.5). As seen among men, risk was higher for women who smoked only black tobacco (OR, 3.8;95% CI, 0.4-38.3) than for those who smoked only blond tobacco (OR, 1.6;95% CI, 0.4-6.0) relative to never smokers. Risk for bladder cancer was only 40% higher for smokers of black tobacco compared with smokers of blond tobacco (OR, 1.4;95% CI, 0.98-2.0)(17).

A case-control study that conducted in France stated that The odds ratio decreased quickly after cessation of smoking among smokers of black tobacco than those with blond tobacco, but the residual risk after cessation was I5 years higher among the former than among the latter. (33)

A case control study that conducted in US showed that people who have only smoked unfiltered cigarettes have higher risks than those who have only smoked filtered cigarettes but that people who have switched from unfiltered to filtered have experienced no reduction in risk(36).

A cohort study was conducted in US showed that Smokers of filtered cigarettes had a slightly reduced risk of bladder cancer relative to smokers of nonfiltered cigarettes (odds ratio 0.64,95% confidence interval 0.38 to I .10 among male smokers; odds ratio 0.74, 95%confidence interval 0 3 7 to 1.48 among female smokers)(44).

3.4 Duration of Smoking

In Prospective Study of 619 cases compared with lifelong nonsmokers the rate ratios (RR) for ex- and current cigarette smokers were 2.1 (95% CI 1.5-3.0) and 3.3 (95% CI 2.4-4.6), respectively. The RR for smoking duration was 1.03 (95% CI: 1.02-1.04) per 1-year increment. The RR per 10 cigarettes/day was 1.3 (95% CI 1.2- 1.4). Tar and nicotine exposure increased bladder cancer risk only weakly. It appeared that associations of cigarette smoking characteristics with bladder cancer risk were largely attributable to cigarette smoking duration only.

A case-control study was conducted in France showed that Starting smoking early in life increased significantly the risk, but no progressive reduction in risk with increased starting age was discernible in the model including this factor in a continuous form. There was no evidence of any significant reduction in risks for ex-smokers, compared to current smokers even for long-term quitters(42).

3.5 Intensity

For both sexes, there was a general increase in the risk of bladder cancer associated with an increase in the number of cigarettes smoked per day and an increase in the number of years of regular smoking. Men who smoked 40 or more cigarettes per day for 20–39 years had an OR of 4.87 (95% CI _ 3.46 to 6.84). For all other smoking categories (No. of cigarettes/day 0,1-19,>20), the ORs for women were higher than for men . For example, in the heaviest smoking category (_40 cigarettes smoked per day for _40 years), the OR in women was more than twice that in men (11.49 versus 5.23, respectively)(19).

A cohort study that was conducted in Iowa, US, showed that risk of BC increase with pack year of cigarette smoking, the RR was 3.58 (95% CI _ 1.86–6.88). There was an increase in the RR of bladder carcinoma as the number of pack-years increased. In the multivariate model, each 20 pack-years increase in smoking was associated with a 1.13-fold increase in the RR of bladder carcinoma (95% CI _ 0.88–1.43)(29).

Another case-control study conducted in Maine, New Hampshire, and Vermont that examined bladder cancer risk in relation to smoking stated that within categories of intensity, odds ratios increased approximately linearly with increasing pack-years smoked, but the slope of the increasing trend declined with increasing intensity. (32)

Another case control study conducted in Germany finds that a significant dose-response relation was observed for increasing cigarette consumption, and a significant decrease in risk was shown for ex-smokers. (34)

Another case control study conducted in US find that the odds ratios for number of cigarettes smoked per day (cpd) increased to approximately 2.5 for smokers of more than 20 cpd, after adjustment for duration and nonsmoking-related covariates. Above 20 cpd, no further increase in odds ratio was observed. (35)

4 Discussion

Cigarette smoking is well-known as a cause of bladder cancer, and smokers have two to three times the risk of nonsmokers(17-19,29-31). Our results indicate that the risk of bladder cancer increases with duration and intensity of smoking(19,29). Several carcinogens may be responsible for the increased bladder cancer risk experienced by smokers, and laboratory evidence suggests that aromatic amines play a prominent role (15). Black tobacco has higher concentrations of N-nitrosamine and 2-napthylamine than blond tobacco(24). Risk for bladder cancer with black tobacco was o 40% higher compared with smokers of blond tobacco (OR, 1.4;95% CI, 0.98-2.0)(17). In addition, blood levels of 4-aminobiphenyl and adducts of several other aromatic amines are higher for smokers of black tobacco than of blond tobacco(37). Lastly, urine mutagenicity is higher among smokers of black tobacco (38,39).

Regarding sex-specific susceptibility of BC, only one case-control study found a significantly increased risk of BC in women who smoke compared to men who smoke a comparable amount of cigarette. Case–control data(19) alone are inadequate to address the question of differential sex-specific susceptibility to tobacco carcinogenesis. However, the outcomes can be strengthened by the addition of corroborating evidence about 3- and 4-ABP– hemoglobin adducts in smoker women. Consistent with differential sex-specific susceptibility to tobacco carcinogens, we noted that women who smoked had statistically significantly greater levels of 3- and 4-ABP–hemoglobin adducts compared with men who smoked similar amounts of cigarettes. Thus, women may experience a higher degree of arylamine activation compared with men and, therefore, have a greater risk of bladder cancer. There is little information on sex-specific patterns of arylamine activation. However, it is interesting to note that glutathione S-transferase M1 (GSTM1), a detoxification enzyme linked to a low risk of bladder can-

cer(40), is more abundant in male than in female mouse livers(41). This experimental result would predict that there is greater arylamine detoxification activity as well as lesser arylamine adduct formation and, subsequently, a lower risk of bladder cancer in male than in female smokers.

5 Conclusion

Cigarette smoking is the best-established, individually modifiable risk factor for bladder cancer development. In most populations, over half of cases in men and a sizable proportion in women are attributable to this habit. Epidemiological studies conducted in different populations have shown a linear relationship between intensity and duration of smoking and risk. Smoking black (air-cured) cigarettes results in a higher risk than smoking blond (flue-cured) tobacco cigarettes; results on inhalation patterns and use of filter are not consistent.Future research regarding the effects of smoking needs to continue to improve our understanding.

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