DOI: https://doi.org/10.61841/58pyv510 Publication URL: https://nnpub.org/index.php/MHS/article/view/2073

# ASSOCIATION OF SMOKING AND BLADDER CANCER: AN UPDATED SYSTEMATIC REVIEW

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## ABSTRACT

***Introduction:*** *Bladder cancer is the 10th most common global cancer, with increasing incidence, primarily linked to smoking, occupational exposures, and genetic factors. This systematic review explores the association between tobacco use and bladder cancer, emphasizing the importance of understanding its multifactorial etiology for effective prevention.*

***Method****: The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.*

***Result****: Our search produced 18 results. After looking at the titles and summaries, we found several papers that fit our criteria. At first, we excluded few articles because they were written in review and case report style. But after reading the full papers carefully, we included five papers in our final analysis. These papers included two-sample univariable and multivariable Mendelian Randomization (MR) analysis, case control study, prospective cohort study of patients with NMIBC diagnosed from 2015 to 2019, experimental study, and rtrospective study.*

***Conclusion:*** *The systematic review involved Mendelian Randomization analysis, underscores smoking as a significant risk factor for bladder cancer, with no evidence linking alcohol consumption to the disease. In a prospective cohort study on Non-Muscle Invasive Bladder Cancer, the study establishes a dose-dependent relationship, emphasizing the urgency for effective smoking cessation interventions in patients, especially those with prolonged smoking history. Additionally, the investigation into molecular pathways reveals the upregulation of the platelet-activating factor (PAF) pathway by cigarette smoke exposure, suggesting PAF-PAF receptor (PAF-R) interaction as a promising therapeutic target for managing bladder cancer growth.*

**Keywords**: *Bladder cancer, cigarette, kidney neoplasm, smoking, tobacco consumption*

## INTRODUCTION

Bladder cancer, also known as urological or urinary bladder cancer, ranks as the 10th most common cancer globally, with a steadily increasing incidence, particularly in developed nations.[1,2] This systematic review aims to comprehensively investigate the association between smoking or tobacco consumption and bladder cancer. Understanding the epidemiological aspects and risk factors related to this malignancy is crucial for prevention efforts. The urinary bladder, a hollow organ in the lower abdomen, primarily functions to store urine received from the kidneys until micturition. The urothelial cells lining the bladder, constantly exposed to potentially mutagenic agents in the urine, contribute to the majority of bladder cancer cases, especially in developed countries.[3,4]

Notably, men exhibit a fourfold higher incidence of bladder cancer, possibly due to increased tobacco smoke and occupational exposures. The relative risk of bladder cancer following tobacco consumption is second only to lung cancer, emphasizing the significance of investigating this association.[5] Despite a decline in tobacco consumption in the US, consistent bladder cancer mortality rates suggest a lag effect from past tobacco exposure.[6,7] Additionally, heritable genetic predispositions are implicated in a fraction of bladder cancer cases, further emphasizing the multifactorial nature of its etiology.[8]

Bladder cancer detection typically occurs through symptoms like hematuria, followed by diagnostic procedures such as cystoscopy, ultrasound, and CT urography. Early-stage diagnoses, constituting a majority, allow for effective resection and improved survival rates. Treatment strategies vary based on the cancer stage, ranging from transurethral resection for non-muscle-invasive cases to radical cystectomy and chemotherapy for muscle-invasive cases. This review consolidates current knowledge on these diagnostic and treatment modalities, contributing to a holistic understanding of bladder cancer management.[9]

While advancements in diagnosis and treatment have improved survival rates, bladder cancer remains a substantial contributor to the global cancer burden, especially in developed nations. Therefore, this systematic review seeks to enhance our understanding of the epidemiology and risk factors associated with bladder cancer, providing valuable insights for preventive strategies and guiding further research directions in the field.

## METHODS

### Protocol

This study adhered to the guidelines outlined in the 2020 Preferred Reporting Items for Systematic Review to ensure alignment with necessary standards, thereby guaranteeing the accuracy of conclusions derived from the investigation.

### Criteria for Eligibility

For this systematic review, the authors systematically compared and evaluated written articles pertaining to risk factors of bladder cancer associated with smoking cigarette and tobacco consumption. Throughout the document, the primary objective was consistently to emphasize the significance of identified risk factors. Data extraction involved consideration of authorship, publication year, study design, sample size, results, and discussion. Primary outcomes focused on variables assessed to establish the main results for risk factors of bladder cancer associated with smoking cigarette and tobacco consumption.

Participating researchers had to meet specific conditions: the paper should be in English and should specifically address the determination of risk factors associated with stunting in toddlers. Published articles meeting the following conditions were included: those published since 2019 within the timeframe relevant to this systematic review. Excluded were studies falling into categories such as editorials, submissions lacking a DOI, already published review articles, and entries essentially mirroring already-published journal papers.

### Search Strategy

Researchers independently conducted a search for relevant articles in databases (PubMed) on February 2024, using specific keywords related risk factors of bladder cancer associated with smoking cigarette and tobacco consumption. The search strategy included MeSH terms, All Fields, and logical operators. Manual searches were also conducted to identify articles meeting the specified criteria, ("cigarette smoking"[MeSH Terms] OR ("cigarette"[All Fields] AND "smoking"[All Fields]) OR "cigarette smoking"[All Fields] OR ("smoking"[All Fields] AND "cigarette"[All Fields]) OR "smoking cigarette"[All Fields]) AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) AND ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]).

### Inclusion and exclusion criteria

The studies included had specific criteria: (1) they needed to be original research related to risk factors of bladder cancer associated with smoking cigarette and tobacco consumption; (2) they could be Randomized Controlled Trials (RCTs) or observational studies (cohort or case-control studies); (3) relevant data had to be accessible. On the other hand, certain

studies were excluded if they: (1) were ongoing or lacked available data; (2) were duplicates, in which case the most recent article was selected; (3) were not in English.

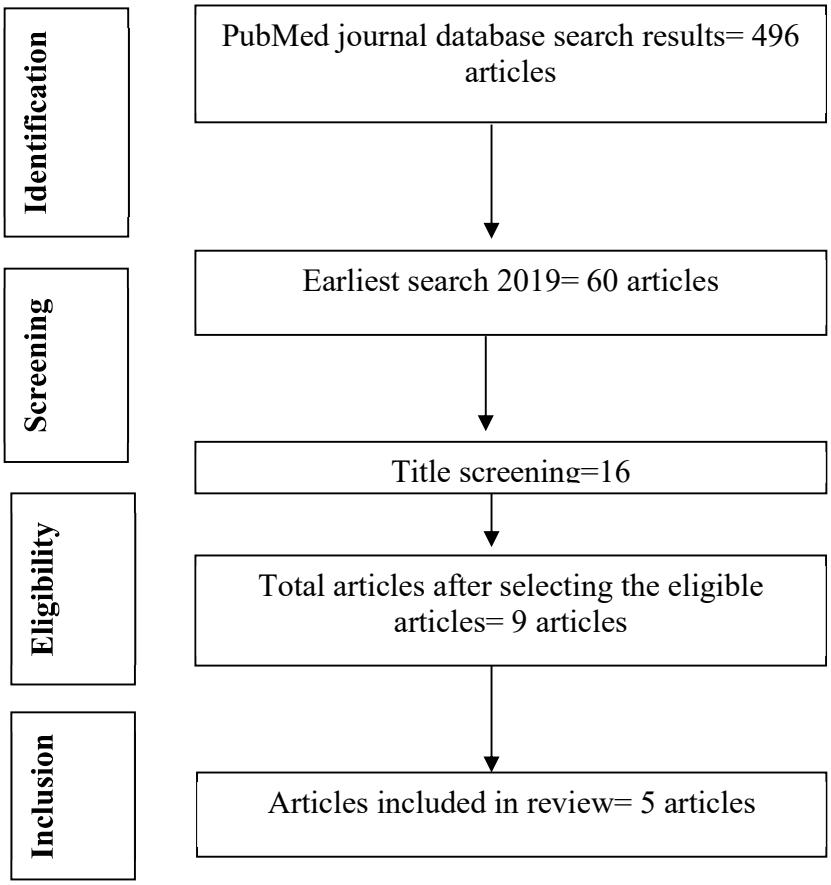


**Figure 1. Article search flowchart**

## Data Retrieval

Following a review of abstracts and titles, the authors evaluated each study's adherence to the inclusion criteria. Subsequently, they chose pertinent studies that met the specified criteria to be included as references in their article. The systematic review exclusively included papers that satisfied all defined inclusion criteria, with findings from studies failing to meet the criteria being excluded. The analysis of research findings encompassed a thorough examination of various aspects of information, such as names, authors, publication dates, geographical locations, study methodologies, and parameters, all aligned with the study's objectives.

| Author | Origin | Method | Sample Size | Result |
|---|---|---|---|---|
| Xiong wt al., 2022.[10] | China | Two-sample univariable and multivariable Mendelian randomization (MR) analysis. | A total of 1115 cases with bladder cancer and 174 006 noncases from FinnGen consortium and 2883 cases with bladder cancer and 417 955 noncases from UK Biobank study were obtained. | Genetic predisposition to cigarettes per day, lifetime smoking index and smoking initiation were positively associated with an increased risk of bladder cancer in both the FinnGen and UK Biobank consortium. The summary odds ratio (OR) of bladder cancer was 1.79 (95% confidence interval [CI], 1.31-2.45; P = .0002), 2.38 (95% CI, 1.45-3.88; P = .0005) and 1.91 (95% CI, 1.46-2.50; P = 1.59 10 06) for one SD increase in the number of cigarettes per day, lifetime smoking index and smoking initiation, respectively. The genetically instrumented number of drinks per week was not associated with bladder cancer (OR = 0.69; 95% CI, 0.44-1.10; P = .1237). Estimates were consistent in multivariable MR analyses by the adjustments of body mass index and education. |
| Kamal et al., 2023.[11] | Egypt | Case Control Study | Study included 100 BC patients attending Minia oncology centre and 100 control | Our results showed that studied BC cases had higher smoking index with mean of 7.77±3.76 compared to controls 3.08±1.88 (P <0.001). Mean duration of years since quitting smoking was significantly higher |

| | | | | |
|---|---|---|---|---|
| | | | subjects matched by age and sex. | in studied controls than in BC cases with mean of 12.8±2.9 and 9.1±2.1 respectively. Smoking index was a risk factor for BC with (OR= 1.29). The most predictable risk factors for BC were recurrent urinary tract infections (OR=7.6), followed by BC family history (OR=6.1), urinary stones history (OR =5.04), schistosomal infection history (OR =4.92), wait long hours to use toilet (OR =2.25), drink coffee (OR =1.32), smoking index (OR= 1.29) and soft drinks (OR=1.08). |
| Kwan et al.. 2022. [12] | US | The Be-Well Study is a prospective cohort study of patients with NMIBC diagnosed from 2015 to 2019. | Total of 1472 patients(mean[SD] age at diagnosis,70.2[10.8% ]years;1129[76.7%] male patients) with NMIBC were enrolled at a mean (SD) of 2.3 (1.3) months after diagnosis. | Longer cigarette smoking duration and more pack-years were associated with higher risk of recurrence in a dose-dependent manner, with the highest risks for patients who had smoked for 40 or more years (HR, 2.36; 95% CI, 1.43-3.91) or 40 or more pack- years (HR, 1.97; 95% CI, 1.32-2.95). There was no association of having ever smoked, being a former or current cigarette smoker, and years since quit smoking with recurrence risk. No associations with pipes, cigars, e-cigarettes, or marijuana were found. Of 102 patients offered a smoking cessation intervention, 57 (53.8%) received an interventions after diagnosis, with female patients more likely than male patients to engage in such interventions (23 of 30 female patients [76.7%] vs 34 of 76 male patients [44.7%]; P = .003). |
| Kispert et al., 2019. [13] | USA | Experimenta l study. | Primary human urothelial cells (HUC) were obtained from ScienCell Research Laboratories (Carlsbad, CA). | the exposure of bladder cancer cells to cigarette smoke extract (CSE) results in increased PAF accumulation and increased expression of the PAF-R. Furthermore, treatment with CSE increases adherence of bladder cancer cells to bladder endothelial cells and could be abrogated by pretreatment with ginkgolide B. Immunohistochemical analysis of tumor biopsy samples from bladder cancer patients who smoked revealed increased PAF and the PAF-R in tumor regions when compared to normal tissue. These data highlight a pathway in bladder cancer that is influenced by CSE which could facilitate primary tumor growth and increase metastatic potential. |
| Ho et al., 2022.[14] | Taiwan | Retrospectiv e study. | This study involved 9,456 patients who had blad- der cancer after matching. | The overall and specific mortality ratio of patients who were ever smokers were 1.15-fold and 1.16-fold, respec- tively, compared with those of never smokers (overall: 95% confidence interval [CI], 1.06–1.26, P = 0.0014; specific: 95% CI, 1.03–1. 03, P = 0.0176). Patients with bladder cancer who smoked and had significantly higher overall and specific mortality rates were those with Charlson Comorbidity Index (CCI)≥3 (overall: P = 0.0119; specific: P = 0.0092), diabetes mellitus (DM; overall: P = 0.0046; specific: P = 0.0419), and non-muscle-invasive bladder cancer (NMIBC; overall: P = 0.0038; specific: P = 0.0014). |

## RESULT

Our search produced 18 results. After looking at the titles and summaries, we found several papers that fit our criteria. At first, we excluded few articles because they were written in review and case report style. But after reading the full papers carefully, we included five papers in our final analysis. These papers included two-sample univariable and multivariable Mendelian Randomization (MR) analysis, case control study, prospective cohort study of patients with NMIBC diagnosed from 2015 to 2019, experimental study, and rtrospective study.

Xiong et al employed a two-sample univariable and multivariable Mendelian Randomization (MR) approach to investigate potential causal associations between genetic predisposition for smoking and alcohol consumption and the risk of bladder cancer.[10]

A total of 21, 126, 360, and 39 SNPs were chosen as instruments for the number of cigarettes per day, lifetime smoking index, smoking initiation, and drinks per week, respectively. These genetic instruments explained 3.7%, 1.2%, 12.1%, and 2.8% of the phenotypical variance, with minimum F-statistics of 32.07, 12.55, 27.71, and 82.93, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) for bladder cancer were standardized. No heterogeneity was observed, and MR-Egger intercept analyses indicated no directional pleiotropy in all analyses. MR-PRESSO analyses found no outliers (all p for Global test >0.05). [10]

Genetic predisposition to cigarettes per day, lifetime smoking index, and smoking initiation showed a positive association with a significantly increased risk of bladder cancer in both the FinnGen consortium and UK Biobank study. The combined odds ratios for bladder cancer were 1.79, 2.38, and 1.91 for one standard deviation increase in the respective traits. Although there was high heterogeneity in the results for cigarettes per day, the associations were consistent in supplementary analyses. The genetically predicted drinks per week did not show any association with bladder cancer in the IVW combined analysis (OR = 0.69; 95% CI: 0.44-1.10; P = .1237). [10]

PhenoScanner search revealed associations of genetic instruments with education and obesity-related traits. After adjusting for potentially related pleiotropy by education and BMI in multivariable IVW analysis, the effect values for cigarettes per day, lifetime smoking index, and smoking initiation changed slightly, but the confidence intervals were greater than 1. High heterogeneity persisted in the results for cigarettes per day and bladder cancer risk. In multivariable IVW analysis, adjusting for cigarettes per day showed an inverse association between genetic liabilities for drinks per week and bladder cancer risk. However, this association was not significant after adjusting for other factors like lifetime smoking index, smoking initiation, or BMI and education jointly. [10]

Among the cases of Kamal et al. study, 77% were males, and 23% were females, matching the control group. A significant difference was observed in smoking patterns between BC patients and controls. Specifically, 56% of BC patients were current smokers compared to 31% of controls, whereas 42% of controls were non-smokers, contrasting with 35% of BC cases ($P < 0.001$). BC cases exhibited a higher smoking index (mean of 7.77±3.76) compared to controls (mean of 3.08±1.88), with statistical significance ($P < 0.001$). The mean duration of smoking years was also significantly higher in BC cases (mean of 17.6±5) compared to controls (mean of 13±3.3) ($P < 0.001$). Furthermore, exposure to secondhand smoke was more prevalent in BC cases (84.1%) compared to controls (40.6%) ($P < 0.001$). The mean duration of years since quitting smoking was higher in controls (mean of 12.8±2.9) compared to BC cases (mean of 9.1±2.1). [11]

When considering different types of bladder cancer (Transitional cell carcinoma (TCC), Squamous cell carcinoma (SCC)), significant differences were found in smoking patterns. The mean smoking index for TCC, SCC, and controls was 4.28±4.41, 5.05±5.24, and 1.63±2.06, respectively, with statistical significance. Additionally, the mean number of cigarettes per day was significantly higher in TCC and SCC groups compared to controls ($P < 0.001$). The mean number of smoking years was also higher in TCC and SCC groups (16.8±4.7 and 18.5±6.1, respectively) compared to controls (13±3.3), with statistical significance. Regarding the mean number of years since quitting smoking, controls had a significantly higher duration (mean of 12.8±2.9) compared to TCC and SCC groups (7.5±2.1 and 10.4±1.1, respectively) ($P=0.002$). The positive history of secondhand smoke exposure varied significantly among TCC, SCC groups, and controls (82.1%, 84.6%, and 40.6%, respectively). [11]

Most Predictive Risk Factors for Bladder Cancer: Recurrent urinary tract infections, BC family history, urinary stones history, schistosomal infection history, prolonged wait times to use the toilet, coffee consumption, smoking index, and soft drink consumption were identified as the most predictable risk factors for bladder cancer. Adjusted odds ratios for these factors ranged from 1.08 to 7.6. The analysis also confirmed that BC cases had a significantly higher smoking index compared to controls ($P < 0.001$). [11]

The Be-Well Study, conducted as a prospective cohort study of patients with non-muscle-invasive bladder cancer (NMIBC), investigates the associations of nutritional, lifestyle, and genetic factors in bladder cancer treatment and outcomes. Patients were recruited from Kaiser Permanente Northern California (KPNC) and Southern California (KPSC) between 2015 and 2019. Inclusion criteria comprised age 21 years or older, the first diagnosis of NMIBC, alive, and not in hospice care. Exclusion criteria included a previous diagnosis of bladder cancer or other cancer within 1 year prior to or concurrent with NMIBC diagnosis. [12]

A total of 1472 NMIBC patients participated in the study, with a mean age at diagnosis of 70.2 years (SD 10.8), predominantly male (76.7%). The majority were diagnosed with low-grade Ta or T1 disease. The mean time from NMIBC diagnosis to baseline interview was 2.3 months. Regarding smoking behaviors, 33.1% were never cigarette smokers, 59.4% were former smokers, and 7.5% were current smokers. Current smokers had the youngest mean age at cancer diagnosis (66.9 years), followed by never smokers (68.4 years) and former smokers (71.6 years; $P < 0.001$). Gender differences were observed, with female participants more likely to be current smokers, while male participants were more likely to be former smokers. Former smokers had a significantly higher mean BMI at diagnosis compared with never and current smokers. Environmental or chemical exposures were more prevalent among current and former smokers compared to never smokers. Current smokers had smoked for a mean of 29.5 pack-years, while former smokers had smoked for a mean of 25.6 pack-years. [12]

More than 10% of never smokers had used other forms of smoked tobacco, and 17.7% reported ever using marijuana. Former and current smokers exhibited higher proportions of other tobacco use, e-cigarette use, and marijuana use. Longer duration of cigarette smoking and higher pack-years were associated with an increased risk of recurrence in both minimally adjusted and fully adjusted models. No associations were observed for other measures of cigarette smoking or other forms of tobacco use. Smoking cessation interventions were examined in 106 participants who were current or recently quit cigarette smokers. Of these, 57 received at least one smoking cessation intervention, while 49 did not receive any intervention. The most common interventions were dispensed prescription medications and wellness coaching. [12]

This study focused on investigating the impact of cigarette smoke on Platelet-Activating Factor (PAF) and its receptor (PAF-R) in bladder cancer cells. The research also explored the effects of inhibiting iPLA2b, the primary isoform responsible for PAF production, on CSE-mediated PAF accumulation in bladder cancer cells. Additionally, the study examined the influence of the PAF-R blocker ginkgolide B on the adherence of bladder cancer cells to the bladder endothelium. Preliminary studies in smokers with bladder cancer were conducted to validate the findings related to PAF accumulation and PAF-R expression. [13]

In vitro studies involving human urothelial and bladder cancer cells revealed significant increases in PAF accumulation after exposure to cigarette smoke extract (CSE). The iPLA2b-selective inhibitor (S)-bromoenol lactone ((S)-BEL) effectively mitigated CSE-induced PAF accumulation, indicating the mediation of this process through iPLA2b. [13]

Furthermore, the study investigated PAF-R expression in bladder cancer cells following CSE exposure. Modest increases were observed in normal urothelial cells (HUC), while bladder cancer cells (HTB-9 and HT-1376) exhibited greater than twofold increases in PAF-R expression. The graded response resembled patterns observed in breast cancer cells, suggesting potential implications for tumor progression. [13]

To assess the impact on bladder cancer invasiveness and transendothelial cell migration, bladder urothelial and tumor cells were incubated with CSE and tested for adherence to human bladder microvascular endothelial cells (HBMEC). Increased cell adherence was observed, and (S)-BEL pretreatment reduced adherence in the presence of CSE. Additionally, pretreatment with ginkgolide B, a PAF-R antagonist, completely blocked cell adherence, indicating therapeutic potential in inhibiting bladder tumor cell transmigration. Human bladder cancer biopsies were analyzed, revealing higher expression of PAF in tumor areas compared to normal urothelium. High-grade tumors exhibited significantly elevated PAF expression. PAF-R expression was also higher in tumor areas compared to normal tissues, with no significant difference between high-grade and low-grade tumor areas. Immunohistochemistry studies further revealed significantly higher expression of iPLA2b in high-grade tumors compared to low-grade tumors, suggesting a potential role in tumor progression and the observed increase in PAF expression. [13]

Smoking has a substantial impact on the clinical management of bladder cancer, prompting a propensity score-matched study with a long-term follow-up period using Taiwan's National Health Insurance Research Database. The investigation compared the risk of overall and specific mortalities in bladder cancer patients with a history of smoking to matched cohorts within this extensive database. The study, comprising 9,456 matched patients with bladder cancer, revealed notable differences between never-smokers and ever-smokers. [14]

The baseline characteristics demonstrated that ever-smokers had a higher incidence of drinking wine and consuming betel nut, as well as a higher prevalence of patients at advanced clinical cancer stages compared to never-smokers. The overall and specific mortality rates were significantly elevated in patients who were ever-smokers compared to never-smokers, indicating a potential association between smoking history and adverse outcomes in bladder cancer. [14]

The adjusted hazard ratios (HRs) for overall and specific mortality rates were 1.15-fold and 1.16-fold higher, respectively, in patients who were ever-smokers compared to never-smokers. Kaplan-Meier plots further illustrated the divergence in mortality trends between the two groups, with significantly higher rates in ever-smokers during the follow-up period. For cancer-specific mortality rates, underweight BMI and MIBC were identified as significant risk factors. [14]

Male ever-smokers exhibited 1.16-fold and 1.17-fold adjusted HRs for overall and specific mortality rates compared to never-smoke male patients. Additionally, ever-smoke bladder cancer patients with a CCI≥3 and those with non-muscle-invasive bladder cancer (NMIBC) showed increased mortality rates compared to their non-smoking counterparts.

Furthermore, comorbidity risks for bladder cancer patients with a history of smoking were explored. Patients with diabetes mellitus (DM) had elevated overall and specific mortality risks, as did those with hypertension for overall mortality. Regardless of subsequent treatments, smoking increased the risk for overall mortality, with significant differences noted in operation and chemotherapy. [14]

## DISCUSSION

In Xiong et al study employing a two-sample Mendelian randomization (MR) approach, researchers investigated potential links between smoking, alcohol consumption, and bladder cancer risk. Our analysis revealed positive associations between cigarettes per day, lifetime smoking index, smoking initiation, and the risk of bladder cancer. However, we did not observe

a statistically significant association between alcohol consumption and bladder cancer risk. These MR estimates remained consistent in magnitude and direction across various exposures and analysis models.[10]

Findings regarding the association between smoking and bladder cancer risk align with previous observational studies. A comprehensive dose-response meta-analysis, including 17 cohorts and 72 case-control studies, identified an increased risk of bladder cancer in former smokers (OR = 1.83) and current smokers (OR = 3.14) compared to never smokers. The risk exhibited a gradual increase with smoking duration, reaching a plateau at 15 cigarettes a day and 50 pack-years. Another meta-analysis, encompassing 11 cohorts, 14 case-control, and 2 nested case-control studies, explored gender-specific bladder cancer risk associated with smoking. The results indicated a higher-than-expected male-female incidence ratio globally, with secondhand smoke contributing to bladder cancer formation. [10]

Multiple studies have elucidated potential mechanisms by which smoking contributes to bladder cancer. The toxic substances in tobacco, such as polycyclic aromatic hydrocarbons and aromatic amines, could induce proliferation of urothelial cells. Cigarette smoke might extract-induced proliferation via specific cellular pathways, and nicotine in tobacco could induce tumor growth through distinct signaling pathways in bladder cancer. [10]

Contrary to smoking, the association between alcohol consumption and bladder cancer risk has been inconsistent in observational studies. Meta-analyses examining overall alcohol consumption found no significant association with bladder cancer risk. However, subgroup analyses based on specific beverages revealed a negative dose-response association with beer and wine consumption. Additional analyses, involving large cohorts, did not find increased bladder cancer risk associated with heavy or moderate alcohol consumption. Notably, a linear association was observed in those consuming alcohol from spirits or liquor. [10]

In Kamal et al study, the age range of subjects in both cases and controls was 53-83 years. Among cases, 77% were males, 23% were females, 55% were from urban areas, and 31% were professionals. Transitional cell carcinoma (TCC) constituted 69% of histopathology in bladder cancer cases, while 21% were squamous cell carcinoma (SCC). The majority (54%) of cases presented with painless hematuria. There were no statistically significant differences in age and gender distribution between TCC cases, SCC cases, and controls. Overall, sociodemographic data showed no association with bladder cancer.[11]

In contrast, another study reported a higher proportion of SCC cases and a younger mean age for SCC compared to TCC. Additionally, a study by Kyritsi et al. revealed a higher incidence of bladder cancer in males, with females presenting later with more advanced stages, especially in non-muscle invasive bladder cancer (NMIBC). Studies indicate a connection between sex steroids and bladder cancer, with postmenopausal women having a higher risk of TCC. Animal studies support this, showing higher incidence in male rats, and human studies demonstrate androgen receptor expression in bladder epithelium. However, further investigation is needed regarding the prognostic significance of androgen receptor expression in human TCC. [11]

Smoking, a well-established risk factor for various cancers, including bladder cancer, was prevalent in 56% of studied bladder cancer patients compared to 31% of controls. The smoking index, cigarettes per day, and duration of smoking were significantly higher in bladder cancer cases. Exposure to secondhand smoke was more common in cases (84.1%) than in controls (40.6%). Despite higher years since quitting smoking in controls, smoking cessation was associated with a reduced risk of bladder cancer. [11]

Tobacco, a source of carcinogenic compounds, leads to DNA damage, supporting gene-smoking interactions. A meta-analysis confirms a strong association between smoking and bladder cancer, with current smokers having a higher relative risk than ex-smokers. Smoking cessation reduces the risk, and a dose-response relationship is observed between smoking intensity and duration with bladder cancer risk. The study underscores the importance of smoking as a major risk factor for bladder cancer, with a significant impact on incidence and progression. [11]

An extensive cohort study conducted by Kwan et al. comprising one of the largest samples of patients with non-muscle invasive bladder cancer (NMIBC), involved 1472 individuals within the KPNC and KPSC integrated health care systems. Among the participants, 59% were former cigarette smokers, and 8% were current smokers at the time of cancer diagnosis. Additionally, 14% reported using pipes or cigars, 4% used e-cigarettes, and 25% used marijuana. The study revealed a dose-dependent association between longer duration of cigarette smoking and higher pack-years with increased risk of NMIBC recurrence. No such associations were observed for other tobacco products, e-cigarettes, or marijuana. Furthermore, an exploratory analysis of smoking cessation interventions at KPNC showed varying participation, with female patients more likely to engage than males. [12]

Contrary to previous studies with mixed results, this research found that being a former or current cigarette smoker at NMIBC diagnosis did not correlate with a worse prognosis. However, an increased lifetime duration and pack-years of cigarette smoking were linked to a higher risk of recurrence. The study suggests that chronic and cumulative smoking exposure to the bladder urothelium before cancer diagnosis may contribute to ongoing susceptibility to tumor

development. The findings emphasize the significance of cumulative smoking exposure over current smoking status in understanding the harmful association with NMIBC prognosis.[12]

Given the potential aggregate effect of smoking on poor health outcomes, the study underscores the importance of smoking cessation in patients with NMIBC. Health care practitioners, particularly urologists, can play a crucial role in improving smoking cessation rates during the treatment of NMIBC patients. The study also highlights the success of the KPNC perioperative smoking cessation program, suggesting the need for a comprehensive evaluation focused on NMIBC patients undergoing surgery to examine the program's effectiveness in recurrence and progression outcomes.[12]

Despite extensive efforts to eliminate tobacco smoking, it remains a significant public health concern, with over 17% of US adults identified as smokers, constituting the leading preventable cause of death and disease.[15] While the association between cigarette smoking and cancers like lung and esophageal has been extensively studied, there is still much to uncover regarding the impact of cigarette smoking on bladder cancer. A recent survey indicated that 94% of urology patients recognized the link between smoking and lung cancer, but only 25% were aware of the association with bladder cancer.[16] Surprisingly, tobacco smoking remains the predominant risk factor for bladder cancer, contributing to almost 50% of bladder cancer cases.[17] Recent cohort studies have noted an increased relative risk for smoking and bladder cancer in the United States, potentially reflecting changes in cigarette composition.[18]

Platelet-activating factor (PAF) is a potent lipid mediator implicated in vascular, inflammatory processes, tumor growth, angiogenesis, and metastasis.[19] Initially associated with smoking due to elevated levels in patient plasma after cigarette smoke exposure[20], PAF's role has been studied in various smoking-related diseases. This study observed significant increases in PAF accumulation in urothelial and bladder cancer cells following exposure to cigarette smoke extract (CSE), with the most pronounced increases in aggressive grade III HT-1376 cells. The findings suggest a potential link between PAF production and the difficulty in treating aggressive bladder cancer, emphasizing PAF as a therapeutic target.[13]

The study proposed that PAF and its receptor might play a role in tumor cell interactions and interactions between tumor cells and endothelial cells. Blocking the PAF receptor (PAF-R) with a natural antagonist, ginkgolide B, resulted in the abrogation of bladder cancer cell adherence to bladder endothelial cells, indicating a potential effect of smoking on tumor progression through cancer cell adherence and transmigration across endothelial cells. This phenomenon was consistent across different cancer types, including breast and prostate cancer. The study suggests that CSE-induced cell adherence via the PAF-PAF-R interaction may represent a general pathway for many cancers.[13]

The study speculates that the increased adherence following CSE exposure and subsequent PAF/PAF-R interaction result from endothelial cell dysfunction in smokers. Endothelial cells, critical for primary tumor establishment and progression to metastatic sites, are known to undergo dysfunction due to cigarette smoking. The complete abrogation of bladder urothelial or tumor cell adherence by ginkgolide B directly implicates the PAF-PAF-R interaction in communication and tumor progression between bladder urothelial/cancer cells and bladder endothelial cells. In-vitro studies with whole cigarette smoke extract were conducted to reflect the typical market cigarette, but further research is needed to identify specific components responsible for PAF and PAF-R changes in these cell lines.[13]

To validate findings from bladder cancer cell lines, the study explored whether similar changes could be observed in bladder cancer patient tissue. While the small sample size limits major conclusions, immunohistochemistry for iPLA2b and PAF revealed increased expression in higher-grade tumor regions compared to low-grade tumors. PAF-R expression was high in both low- and high-grade tumors, suggesting that differences in PAF-mediated effects between tumor grades are likely mediated via increased PAF content. The study highlights a pathway upregulated in bladder cancer influenced by CSE, with potential implications for primary tumor growth and increased metastatic potential. Targeting the PAF-PAF-R interaction could be a valuable therapeutic approach for managing further tumor growth, providing novel insights into bladder cancer pathogenesis.[13]

Bladder cancer is a prevalent global malignancy, with previous research suggesting a correlation between cigarette smoking and adverse initial diagnostic parameters. While past studies primarily focused on the impact of smoking on recurrence risk in patients undergoing transurethral resection of bladder tumors (TURBT) for non-muscle invasive bladder cancer (NMIBC) or radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC), a gap in understanding the association with overall or cancer-specific mortality persisted. This study addresses this gap, revealing that individuals who ever smoked exhibited higher clinical stages at initial diagnosis ($P = 0.0006$) and significantly worse overall and specific mortality rates ($P = 0.002$ and 0.017, respectively) compared to never-smokers.[14]

Subgroup analyses in NMIBC and MIBC demonstrated increased overall and specific mortality rates for ever-smokers in NMIBC ($P = 0.0039$ and 0.0015, respectively). While MIBC patients who were ever-smokers showed a comparable outcome, with a 1.12-fold increase in overall mortality and a 1.07-fold increase in cancer-specific mortality, the differences were not statistically significant ($P = 0.0553$ and 0.3669, respectively). Additionally, ever-smokers undergoing TURBT for NMIBC exhibited worse overall and cancer-specific mortality rates than never-smokers ($P = 0.0069$ and 0.0026, respectively). Notably, cigarette smoking did not significantly impact any treatment in MIBC.[14]

Bladder cancer is recognized as a complex and heterogeneous disease, necessitating subset analyses considering various clinical stages and treatment modalities. The study identified risk factors associated with overall and cancer-specific mortalities in bladder cancer patients who were ever-smokers, indicating significantly higher mortality rates, particularly in men, those with a Charlson Comorbidity Index (CCI) ≥3, those with comorbid diabetes mellitus (DM), and those with NMIBC. Sex-specific effects of smoking were observed, with ever-smoke men exhibiting significantly higher overall and specific mortality rates than their never-smoke counterparts. [14]

Notably, for women with bladder cancer, overall and specific mortality rates were higher than in men, but the differences were not significant. However, ever-smoke men with bladder cancer showed significantly higher overall and specific mortality rates than never-smoke men. The CCI, a tool for calculating comorbidities and mortality risk, indicated a higher mortality rate in ever-smoke patients. DM, recognized as a risk factor for bladder cancer, exhibited a multiplier effect, significantly increasing overall and specific mortality rates in ever-smoke patients. [14]

## CONCLUSION

The systematic review, presents compelling evidence supporting smoking as a significant risk factor for bladder cancer. The study conducted a comprehensive Mendelian Randomization (MR) analysis, revealing a strong association between smoking and bladder cancer, while finding no supporting evidence for a link between alcohol consumption and bladder cancer risk. Further exploration in a prospective cohort study focused on Non-Muscle Invasive Bladder Cancer (NMIBC) emphasized the critical role of cigarette smoking in disease recurrence. The study demonstrated a dose-dependent relationship, indicating that both longer duration of smoking and increased pack-years were associated with a higher risk of NMIBC recurrence. Notably, patients with 40 years or more of smoking exhibited a twofold higher risk of recurrence, emphasizing the urgency for effective smoking cessation interventions in NMIBC patients.

An investigation into the molecular pathways involved in bladder cancer highlighted the upregulation of the platelet-activating factor (PAF) pathway influenced by cigarette smoke exposure (CSE). This pathway potentially facilitates primary tumor growth and enhances metastatic potential. Targeting the PAF-PAF receptor (PAF-R) interaction emerged as a promising therapeutic strategy for managing tumor growth. The study acknowledges the need for future research to uncover distinct pathways responsible for specific outcomes and to elucidate the intricate interaction between bladder endothelial cells and cancer cells in vivo.

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