RESEARCH ARTICLE

Effect of smoking on the recurrence and progression of non-muscle-invasive bladder cancer

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Abstract

Background It is well established that smoking is the most significant risk factor for bladder cancer, yet the impact of smoking on the recurrence and progression of non-muscle-invasive bladder cancer (NMIBC) remains a contentious issue.
Objective To review all relevant literature published to date, providing a comprehensive assessment of the effects of smoking on the recurrence and progression of NMIBC, thereby offering a basis for smoking cessation management in NMIBC patients.
 Methods A search was conducted for all relevant literature published up to April 2024 in PubMed, Web of Science, and Embase databases. The existing literature results and deficiencies were analyzed, and the gaps in understanding between different studies were highlighted, with recommendations for future research.
Results A total of 24 studies were included in this work. Among them, 14 studies suggested that smoking promotes the recurrence and progression of NMIBC, while another 10 studies concluded that smoking has no effect on the recurrence and progression of NMIBC patients.
Conclusions Our research indicates that smoking increases the risk of recurrence and progression in NMIBC patients, and quitting smoking can improve health-related quality of life. High-quality, large-sample prospective cohort studies (or randomized controlled studies) are still needed in the future.

Keywords Smoking · NMIBC · Recurrence · Progression

Introduction

With more than 6,10,000 new cases expected to be diagnosed in 2022—more than 3.1% of all cancer-related fatalities globally—bladder cancer (BCa) is the ninth most frequent malignancy, according to GLOBOCAN [1]. Non-muscle-invasive bladder cancer (NMIBC) accounts for 75% to 85% of bladder cancer cases [2]. Within 5 years, 10% to 15% of tumors advance to muscle-invasive bladder cancer (MIBC), and recurrence rates for NMIBC patients range from 50 to 70% [3–5]. BCa is the most financially demanding cancer due to its costly surgical care and ongoing monitoring [6].

As it increases the risk by two to four times, smoking is now the most well-established risk factor for BCa [7]. It is unknown, however, how smoking affects relapse and progression in NMIBC patients. According to recent research, smoking has a detrimental effect on oncologic outcomes for individuals who have non-smoking-related cancers such as prostate cancer [8] as well as other smoking-related cancers, including lung [9] and renal cell carcinoma [10]. A growing amount of literature has examined the impact of smoking on the recurrence and progression of NMIBC; however, the findings have been mixed as research continues to be conducted. We examined pertinent research up until April 2024, discussed and evaluated the findings of previous studies, and studied pertinent literature in order to completely evaluate the effects of smoking and quitting on recurrence and progression in patients with NMIBC.

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There is conflicting evidence about the relationship between smoking and patient outcomes. While some studies have linked heavy, long-term smoking to lower relapse-free survival [11–15] and invasiveness [11, 15–20]. In addition, other research indicates that there is no connection between smoking and patient outcomes [21–23]. These investigations were constrained by retrospective cohort studies, unreliable exposure evaluations, and small sample sizes. There are few prospective cohort studies, which are also limited by the small sample size and short follow-up time. Furthermore, different studies observed different outcome measures and defined relapse and progression differently. This makes it challenging to compare the outcomes consistently. Generally speaking, the majority of research supports the idea that smoking contributes to the development and recurrence of NMIBC. Future research must be backed by high-quality, large-sample randomized controlled trials due to the current lack of strong evidence.

Next, we discussed the connection between smoking and BCa based on the etiology of the disease, followed by the description of our strategy for searching the literature, an analysis of the literature's findings and limitations based on the type of study (retrospective cohort study, prospective cohort study, randomized controlled study (RCT), systematic review, and meta-analysis), and lastly an inductive summary of the body of known research. Future research recommendations are also suggested.

The epidemiology of bladder cancer

Incidence and mortality of bladder cancer

BCa is sixth in males and thirteenth in death among all cancers worldwide, with women ranking tenth in terms of cancer incidence. There were 2,20,000 bladder cancer deaths and 6,14,000 new cases reported globally in 2022 [1]. The age-standardized incidence and mortality rates were 2.4/100,000 for women and 3.1/100,000 for men, respectively [1]. Regional differences were seen in age-standardized morbidity and mortality rates; mortality rates were greater in developing regions than in developed regions, and the highest incidence rates were found in southern Europe, western Europe, and North America, in that order [1].

Etiology of bladder cancer

Smoking

Approximately half of BCa cases are related to smoking, making it the most well-established risk factor for the disease [24–26]. The risk of BCa is directly correlated with time and can increase by two to three times with smoking [7]. Still, increasing the intensity of smoking did not substantially raise the risk of BCa once it reached 15 cigarettes per day (or 50 packs annually). In addition, the risk was much lower for smokers who had stopped more than 20 years prior to the diagnosis, although it did not go down immediately after stopping. However, the risk of BCa remained elevated by 50% even for individuals who stopped smoking more than 20 years earlier [26].

Chemical product exposure

A significant risk factor for BCa is prolonged exposure to industrial chemicals such as chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, and aromatic hydrocarbons [27]. Workplace exposure to chemicals, dyes, rubber, pharmaceutical preparations, textiles, paint, and pesticides is responsible for about 20% of BCa cases [28]. Paint workers are also at a heightened risk of developing bladder cancer. Studies on the epidemiology of BCa have shown that the incidence of the disease is lower in farmers, gardeners, teachers, and other jobs, and greater in business and administrative staff, male electricians, and electronics workers [28, 29].

Race

BCa is also significantly influenced by race; non-Hispanic Caucasians have the highest prevalence, around twice as high as African Americans; however, racial disparities were only observed in non-muscle-invasive tumors, which had comparable rates [30]. Adverse pathology is more common in African Americans, and their disease-specific survival is lower [31, 32].

Other factors

Other potential risk factors include a history of pelvic radiation therapy [33], use of the chemotherapy medication cyclophosphamide [24], drinking water contaminated with high amounts of arsenic or arsenic over an extended period of time [34], and chronic infections (bacterial, schistosomiasis, and HPV infections) [24, 35]. Furthermore, a family history of the condition doubles the risk of BCa [36], which may possibly be linked to genetic factors. There was no statistically significant correlation found between drinking alcohol and developing BCa. Although the exact relationship between a high fruit and vegetable diet and a low risk of BCa is unknown [33, 37, 38], a high intake of fat, cholesterol, fried meals, and red meat may raise the risk of BCa [28].

Genomic variation

DNA mutations in healthy bladder cells are the first step toward malignant alterations. BCa is frequently caused by chemical carcinogens, such as 2-naphthylamine, 4-aminobenzene, and others. Urine contains carcinogenic substances that cause malignant alterations in bladder epithelial cells, and tobacco metabolites are discharged in it. HER-2, HRAS, Bcl-2, FGFR3, C-myc, MSH2, APE1, GTSEI, and other bladder-related oncogenes are among the oncogenes that are currently the subject of the majority of research on the genesis of BCa [39–45].

Materials and methods

Retrieval strategy

To obtain relevant literature, we searched PubMed, Web of Science, and Embase databases for articles published up to April 2024. The search terms are as follows: "((progression OR progression-free survival OR muscle-invasive) AND (non-muscle invasive bladder cancer OR NMIBC) AND (Risk factors OR Smoking OR smoke OR cigarette OR tobacco)) OR ((progression OR recurrence-free survival OR muscle-invasive OR recurrence) AND (non-muscle invasive bladder cancer OR NMIBC) AND (Smoking OR smoke OR cigarette OR tobacco))" and "(recurrence OR progression OR survival) AND (non-muscle invasive bladder cancer OR NMIBC) AND (Smoking OR smoke OR cigarette OR tobacco)".

Research selection

Once redundant literature has been eliminated, the two writers (VV and MDR) individually examine the entire text to assess eligibility; if there is disagreement, the third researcher (SC) is consulted before a consensus is resolved. For additional pertinent references, we then searched through all of the identified papers, reviews that had already been published, and meta-analyses. Listed below are the inclusion criteria: Works addressing how smoking affects relapse and progression in NMIBC patients that provide measures of statistical uncertainty (such as standard error, variance, or exact P-values) or hazard ratios (HR) and 95% confidence intervals (CI). Excluded from consideration was any literature that disclosed smoking status alone, without mentioning smoking intensity or duration, or that disclosed smoking intensity or duration alone. The risk of tumor development or recurrence is the main outcome. The first time a bladder tumor returns is known as a disease recurrence. The upper urinary tract tumor is considered a second

primary tumor rather than a tumor recurrence [13]. Any bladder tumor that reaches stage T2 or above is considered to have progressed [13].

Smoking-related indicators and their concepts

The variables related to smoking included: smoking status; average number of cigarettes smoked per day (CPD; that is, amount: 1–9, 10–19, 20–29, ≥ 30); length of smoking (≤ 9.9, 10–19.9, 20–29.9, 30–39.9, ≥ 40 years); and time to stop smoking (≤ 4.9, 5–9.9, ≥ 10 years). The categories of smoking status include smokers (> 100 cigarettes, non-negligible lifetime number of cigarettes) and never smokers (< 100 cigarettes) [13]. Smokers can continue to be classified as quitters (who stopped smoking 1 year before diagnosis), former smokers (who quit between 1 year before diagnosis and 3 months after diagnosis), and current smokers (who continue to smoke after diagnosis). Former smokers and current smokers are the most common categories of smokers.

At the time of diagnosis, smoking history was frequently evaluated through self-report [13]. Cumulative smoking exposure is the result of CPD after years of smoking. Smokers were categorized into four categories of lifetime cumulative smoking exposure based on the amount and duration of their smoking: mild short-term (< 20 CPD and < 20 years), mild long-term (< 20 CPD and ≥ 20 years), heavy short-term (≥ 20 CPD and < 20 years), and heavy long-term (≥ 20 CPD and ≥ 20 years) [8, 13, 46].

Result

Retrospective cohort studies

Smoking promoted the recurrence and progression of NMIBC (the difference was statistically significant)

In Rink et al.'s report, 91 non-smokers, 192 former smokers, and 107 current smokers were enrolled, with a median follow-up of 66 months [47]. Univariate analysis revealed that among ever smokers, increasing smoking intensity ($p \leq 0.015$), duration ($p < 0.001$), and cumulative exposure ($p < 0.001$) were associated with an increased risk of illness recurrence and progression [47]. In multivariate analysis, cumulative smoking exposure showed an independent risk factor for progression and relapse ($p < 0.003$). When compared to present smoking, quitting smoking more than ten years before treatment was independently linked to a lower rate of relapse (HR 0.4, $p < 0.001$). In addition, current smokers had a lower survival rate than former smokers, and former smokers had a lower survival rate than never smokers ($p > 0.05$). In a related study, there were 2043 primary NMIBC patients with a median follow-up of 49 months (24%

never smokers, 47% former smokers, and 29% current smokers, respectively) [13]. In multivariate analysis, smoking status was also linked to the cumulative incidence of illness progression ($p = 0.003$). In smokers who are currently or were previously smokers, cumulative smoking exposure was linked to both disease progression and relapse ($p < 0.001$). Giving up smoking for more than ten years decreased the chance of advancement (HR: 0.42; 95% CI 0.22–0.83; $p = 0.036$) and relapse (HR: 0.66; 95% CI 0.52–0.84; $p < 0.001$). According to Kashif et al., smokers and non-smokers were equally divided among the 64 patients, and they were followed for an average of 28.36 months. The likelihood of tumor growth was four times higher in smokers than in non-smokers [48]. There were 64 non-smokers, 64 former smokers, 59 ex-smokers, and 78 continuing smokers. The median follow-up was 38 months. For current and former smokers, the 3-year relapse-free survival rates were 45% and 70%, respectively, in Chen et al.'s findings [49]. One hundred sixty-eight patients (34.7%) had never smoked, 121 patients (25%) were current smokers, and 195 patients (40.3%) were former smokers. The median follow-up was 25 months. In addition, cumulative smoking exposure was found to be significantly ($p < 0.001$) linked with tumor recurrence in both present and past smokers by Li et al [50]. Patients who had quit smoking for at least 10 years had a decreased risk of tumor recurrence compared to current smokers (HR: 0.456, $p = 0.007$) [50]. According to Ogihara et al., 181 patients (28.5%) were classified as current smokers, 154 (24.3%) as former smokers, and 299 (47.2%) as non-smokers. The rates of tumor recurrence were considerably lower in non-smokers than in smokers ($p < 0.001$ and $p < 0.001$, respectively) than in smokers [51]. Patients with a 15-year or longer smoking cessation history had significantly decreased tumor recurrence rates ($p < 0.001$). According to Andrade et al.'s report [52], 132 patients with pT1 NMIBC were followed for an average of 76 months. Smoking load had a substantial impact on progression (HR: 1.034, 95% CI 1.016–1.052; $p = 0.0002$) and relapse (HR: 1.019, 95% CI 1.008–1.030; $p = 0.0004$) (Table 1).

Smoking promotes the recurrence and progression of NMIBC (no statistically significant difference)

Although the difference was not statistically significant, the study by Fleshner et al. found that current smokers had lower relapse-free survival than either quitters or ex-smokers (127 former smokers, 51 ex-smokers, and 108 current smokers) [11]. Similarly, Matulewicz et al. found that of the 723 NMIBC patients included, 34.7% were nonsmokers, 52.6% were past smokers, and 12.7% were current smokers. Smoking status was not substantially linked with relapse during the three-year trial period [23]. The study population included 181 never smokers (18.8%), 490 former smokers

(50.9%), and 292 current smokers (30.3%) at diagnosis. Follow up for 5 years. The risk of relapse or progression was not shown to differ statistically significantly across never, former, or current smokers, according to Grotenhuis et al [53]. The categories of smoking quantity, duration, and cumulative exposure linked to the prognosis of NMIBC also showed no dose–response correlations. The likelihood of a relapse and its advancement were not significantly affected by the quit date [53]. Three huyndred eighty-six patients (62.0%) were former smokers, 97 patients (15.6%) were current smokers, and 140 patients (22.5%) had never smoked. The median follow-up was 80.9 months. Any definition of smoking status did not correlate with relapse or advancement in the Sfakianos et al.'s report [54]. Similar results were found by Michalek et al., who found that of 302 patients, 32% were non-smokers, 22% were past smokers, and 46% were current smokers. Twenty-three months was the median follow-up time. Neither the number of tumor recurrences nor recurrence-free survival were correlated with smoking status [55] (Table 1).

Result and deficiency

Seven of the aforementioned twelve retrospective cohort studies found a statistically significant increase in the risk of recurrence and/or advancement in patients with NMIBC associated with smoking [13, 47–52]. According to five reports [11, 23, 53–55], smoking had no impact on the rate of recurrence or advancement in NMIBC patients. The constraints inherent in retrospective cohort studies cannot be overcome by any of the aforementioned investigations. Treatment postponement, TURBT repetition, TURBT quality, and adjuvant regimen following TURBT inability to be regulated. Furthermore, it was unable to regulate other tobacco products or other tobacco-exposure scenarios (such as smoking marijuana, cigars, or secondhand smoke). Despite difficulties in data collection, tobacco products of different types and brands differ in tar volume, smoke nicotine volume, and carbon monoxide volume, which may lead to differences in tumor recurrence and progression between patients. Patients self-report their smoking history, making it susceptible to recall bias and fraudulent reporting. Ultimately, people who stop smoking and then pick up again or who smoke continuously cannot be controlled.

Smoking is a dynamic process that takes exposure to smoke into account in addition to smoking status. The only factors that differed between current smokers and never smokers and ex-smokers, respectively, were smoking and quitting. It is inappropriate to compare ex-smokers to never-smokers since there is a dual variable—smoking and quitting—rather than a single variable separating the two groups. Therefore, when follow-up is too short, it is typical to find no differences in recurrence and advancement rates among

Table 1 Effect of smoking on the recurrence and progression of NMIBC: retrospective cohort studies

Author	Smoking status	Smoking exposure	Recurrence and progression	Case	Key findings
Matulewicz [23]	Former smoker (52.6%), current smoker (12.7%), and never smoker (34.7%)	NA	Recurrence	723	Smoking status was not significantly associated with relapse during the 3-year study period.
Rink [47]	Former smoker (192), current smoker (107), and never smoker (91)	Number of cigarettes smoked per day, years of smoking duration, and years of quitting	Recurrence and progression	390	The median follow-up was 66 months. There was no difference in the risk of illness recurrence or advancement among present, ex-, and never smokers. Former smokers' risk of illness recurrence and progression rose with smoking intensity ($p \leq 0.015$), duration ($p < 0.001$), and cumulative exposure ($p < 0.001$). Cumulative smoking exposure was found to be an independent risk factor for illness recurrence and progression ($p \leq 0.003$). Quitting smoking for more than 10 years before treatment was linked to a decreased risk of illness recurrence compared to current smoking (HR 0.4, $p < 0.001$).
Rink [13]	Former smoker (47%), current smoker (29%), and never smoker (24%)	Number of cigarettes smoked per day, years of smoking duration, and years of quitting	Recurrence and progression	2043	The median follow-up was 49 months. Smoking status was linked to the cumulative incidence of illness progression in multivariate analysis ($p = 0.003$). Smoking cumulative exposure was linked to overall survival ($p < 0.001$), disease progression ($p < 0.001$), and recurrence ($p < 0.001$). Over a 10-year period, smoking cessation was associated with a lower risk of disease progression (HR: 0.42; 95% CI 0.22–0.83; $P = 0.036$) and recurrence (HR: 0.66; 95% CI 0.52 to 0.84; $p < 0.001$).
Fleshner [11]	Former smokers (127), ex-smokers (51), and current smokers (108)	NA	Recurrence	286	Multivariate analysis showed that recurrent smokers had lower relapse-free survival compared to former smokers or former smokers.

Table 1 (continued)

Author	Smoking status	Smoking exposure	Recurrence and progression	Case	Key findings
Grotenhuis [53]	Former smokers (490), current smokers (292), and never smokers (181)	Number of cigarettes smoked per day, years of smoking duration, and years of quitting	Recurrence and progression	963	Follow up for 5 years. There were no statistically significant differences or trends in the risk of recurrence or advancement between nonsmokers, former smokers, and current smokers. Furthermore, there was no dose–response relationship with NMIBC prognosis in the categories of smoking volume, duration, or cumulative exposure. There was no significant relationship between quitting duration (≥10 years before diagnosis, <10 years before diagnosis, and current smoker at diagnosis) and risk of relapse or progression.
Kashif Khan [48]	Smokers (32) and non-smokers (32)	NA	Recurrence and progression	64	After an average follow-up of 28.36 months, smokers were four times more likely to have tumor progression than non-smokers.
Chen [49]	Never smokers (64), former smokers (64), ex-smokers (59), and current smokers (78)	NA	Recurrence	265	The median follow-up was 38 months. Current smokers, nonsmokers, ex-smokers, and quitters had 3-year relapse-free survival rates of 45%, 57%, 62%, and 70%, respectively. Relapse risk was comparable for ex-smokers but lower for those who were still smoking or for non-smokers.
Li [50]	Never smokers (168), current smokers (121), and former smokers (195)	Number of cigarettes smoked per day, years of smoking duration, and years of quitting	Recurrence	484	The median follow-up period was 25 months, and smoking did not affect tumor recurrence ($p = 0.063$). Current and past smokers' cumulative smoking exposure was substantially linked with tumor recurrence ($p < 0.001$). Patients who had quit smoking for ≥10 years had a decreased risk of tumor recurrence than current smokers (HR: 0.456, $p = 0.007$).

Table 1 (continued)

Author	Smoking status	Smoking exposure	Recurrence and progression	Case	Key findings
Ogihara [51]	Current smokers (181), former smokers (154), and non-smokers (299)	Number of cigarettes smoked per day, years of smoking duration, and years of quitting	Recurrence	634	Follow up for 5 years. Non-smokers had considerably decreased tumor recurrence rates compared to present and past smokers ($p < 0.001$, respectively). The rate of tumor recurrence was unrelated to smoking intensity or duration. Patients with a ≥ 15-year abstinence duration had considerably reduced tumor recurrence rates than their counterparts ($p < 0.001$). A smoking cessation time of less than 15 years (HR: 2.20; $p = 0.003$) was identified as an independent risk factor for tumor recurrence in the former smoker subgroup.
Andrade [52]	Current smokers, former smokers, and non-smokers	Average number of cigarettes smoked per day, years of smoking duration, and years of quitting	Recurrence and progression	132	Median follow-up was 76 months. Smoking load significantly affected recurrence (HR: 1.019, 95%CI 1.008–1.030, $p = 0.0004$) and progression (HR: 1.034, 95%CI 1.016–1.052, $p = 0.0002$) but did not affect survival. For each additional year, the risk of recurrence and progression increased by 1.9% and 3.4%, respectively.
Sfakianos [54]	Current smokers (97), former smokers (386), and non-smokers (140)	NA	Recurrence	623	The median follow-up was 80.9 months. In both univariate and multivariate analyses, any defined smoking status was not associated with disease recurrence or progression.
Michalek [55]	Current smokers (46%), former smokers (22%), and non-smokers (32%)	NA	Recurrence	302	Median follow-up was 23 months. Smoking status was not associated with recurrence-free survival or the number of tumor recurrences.

never-smokers, ex-smokers, and current smokers. Because of this, the Rink et al.'s study continues to be the best retrospective study [13]. Numerous other studies have not encountered a dead end when it comes to qualitative analysis, and their findings also have some guidance and reference value [47–52]. It is astounding that in Chen et al.'s study [49], quitting smokers had a lower chance of relapsing than did continuing smokers and nonsmokers. Although the authors provide explanations, it is possible that people who stop smoking avoid being exposed to more smoking-related carcinogens. Nonsmokers have been exposed to other, mainly unknown carcinogens, or nonsmokers' genetic makeup predominates in carcinogenic environments. It goes without saying that this explanation is implausible. The small sample size and brief follow-up period of Andrade et al.'s study limit the application of its findings [52]. Furthermore, all of this research is ensnared in the qualitative analysis trap [11, 23, 53–55]. Homogeneous analysis from the source was not possible in Matulewicz et al.'s report because initial NMIBC accounted for only 11.5% and recurrent NMIBC accounted for 88.5% [23]. The impact of smoking on relapse rates is primarily obscured by the high risk, recurrent nature of the disease, and a significant selection bias. People who stopped smoking within a year after receiving a diagnosis were classified as quitters in Grotenhuis et al.'s report [53], but only smoking exposure before the diagnosis was taken into account for current smokers. This means that constant smokers and those who are trying to quit almost exactly coincide. It is obviously illogical to confuse quitting and chronic smokers, even though the simple qualitative analysis has little reference significance.

Prospective cohort studies (or RCTs)

Smoking promoted the recurrence and progression of NMIBC (the difference was statistically significant)

According to Lammers et al.'s [12], of the 718 NMIBC patients included, 121 were non-smokers, 359 were former smokers, and 238 were current smokers. The average follow-up was 2.5 years. In univariate analysis, past and present smokers had considerably shorter RFS ($p = 0.005$). When predicting RFS using multivariate analysis, smoking status remained a significant predictor. 97 patients (24.6%) had never smoked, and 298 patients (75.4%) were smokers. The median follow-up was 48 months. 69.1% and 74.2% ($p = 0.16$), 13.6 and 14.2 months ($p = 0.27$), and 64.0% and 71.3% ($p = 0.08$) were the median times to 3-year RFS, RFR, and first relapse for smokers and never-smokers, respectively, in Serretta et al.'s RCT [22]. Smoking was found to be the primary predictor of relapse ($p = 0.04$) in multivariate analysis [22]. However, in the study by Kwan et al., 874 patients (59.4%) were former smokers, and 111

patients (7.5%) were current smokers. Sixty-seven patients (13.7%) used only pipes and/or cigars; 65 patients (4.4%) used e-cigarettes; and 363 patients (24.7%) used marijuana [56]. The follow-up was 26.4 months. The risk of relapse rose dose-dependently with smoking duration and the number of pack-years smoked. Patients who smoked for more than 40 years (HR, 2.36; 95% CI 1.43–3.91) or more than 40 pack-years (HR, 1.97; 95% CI 1.32–2.95) had the highest risk of recurrence [56] (Table 2).

Smoking promotes the recurrence and progression of NMIBC (no statistically significant difference)

According to Furberg et al., biochemical tests were performed to verify smoking exposure in 354 patients with NMIBC. Of these, 78% were former smokers and 22% were current smokers, with a median follow-up of 3.6 years. The study found that there is no correlation between smoking after diagnosis and the likelihood of relapsing (HR: 0.73, 95% CI 0.45–1.20) [57]. Of the 722 patients with NMIBC included, 103 were never smokers, 266 were former smokers, 186 were current smokers, 150 were former smokers who resumed smoking, and 17 were smokers who quit after diagnosis. During a median follow-up period of 4.21 years, 403 pathologically confirmed NMIBC recurrences occurred in 210 patients. Compared to continuing smokers, only 25 current smokers at diagnosis quit smoking during follow-up (14%) [58]. Relapsing was not less likely in van Osch et al.'s report if smoking was stopped following diagnosis than if it was continued ($p = 0.352$) [58]. In line with the findings of Serretta et al., a total of 194 patients were diagnosed; 67 (34.5%) of them stopped smoking, while 127 (65.5%) did not. At the 38-month median follow-up, the recurrence rates for former and continuing smokers were 49.2% and 60.3%, respectively, and the 3-year RFS was 50.7% and 42.3%, respectively ($p = 0.55$) [59]. Recurrence, the clinical characteristics of the original tumor, and the patients' post-diagnosis smoking behaviors did not show any statistically significant correlation. The number of cigarettes smoked per day and the length of time (years) had no statistically significant impact on the results. Multivariate analysis showed no significant reduction in tumor recurrence following smoking cessation at diagnosis (Table 2).

Result and deficiency

Three of these six Prospective cohort studies showed statistically significant differences in the effects of smoking on relapse and/or progression in patients with NMIBC [12, 22, 56]. Smoking had no effect on recurrence or advancement in patients with NMIBC, according to three trials [57–59]. Although it is a Prospective cohort study, Lammers et al.'s report is very representative [12], with the

Table 2 Effect of smoking on the recurrence and progression of NMIBC: prospective cohort studies

Author	Smoking status	Smoking exposure	Recurrence and Progression	Case	Key findings
Lammers [12]	Ex-smokers (359), current smokers (238), and non-smokers (121)	Number of cigarettes smoked per day, smoking years, and quitting years	Recurrence	718	The median follow-up period was 2.5 years. In univariate analysis, the RFS of former and current smokers ($p=0.005$) was significantly shortened. Smoking status remained a significant predictor of RFS in multivariate analyses.
van Osch [58]	Former smokers (266), current smokers (186), resumed smokers (150), smokers who quit after diagnosis (17), and never smokers (103)	Number of cigarettes smoked per day, smoking years, and quitting years	Recurrence	722	The median follow-up period was 4.21 years, and smoking cessation after diagnosis did not reduce the risk of recurrence ($p=0.352$).
Serretta [22]	Smokers (298) and never smokers (97)	Number of cigarettes smoked per day, smoking years, and quitting years	Recurrence and progression	395	Median follow-up was 48 months. 69.1% and 74.2%, and 13.6 and 14.2 months, respectively, were the 3-year RFS, RFR, and median time to first relapse for smokers and never-smokers, respectively. The primary predictive predictor for relapse in these patients, as revealed by multivariate analysis, was smoking status ($p=0.04$). The probability of relapse was the same for current and former smokers after three years.
Kwan [56]	Former smokers (874) and current smokers (111)	Number of cigarettes smoked per day, smoking years, and quitting years	Recurrence and progression	985	The follow-up was 26.4 months. The risk of relapse increases with smoking duration and number of pack years, in a dose-dependent way: patients with smoking duration $\geq$40 years (HR, 2.36; 95%CI 1.43–3.91) or $\geq$40 packet years (HR, 1.97; patients with 95%CI 1.32–2.95) had the highest risk. Years after quitting, years of continuous or past smoking, and years after stopping were not linked to recurrence risk.
Furberg [57]	Former smokers (78%) and current smokers (22%)	Number of cigarettes smoked per day, smoking years, and quitting years	Recurrence and progression	354	Median follow-up was 3.6 years. There was no association between smoking exposure and the risk of recurrence after diagnosis (HR: 0.73, 95% CI 0.45–1.20).
Serretta [59]	Former smokers (67) and current smokers (127)	Number of cigarettes smoked per day, smoking years, and quitting years	Recurrence and progression	194	After 38 months of follow-up, no statistically significant connection was found between recurrence, primary pathologic characteristics, and smoking habits. The intensity (cigarettes per day) and length (years) of smoking had no statistically significant effect on the results. In multivariate analysis, smoking cessation at diagnosis had no significant effect on tumor recurrence.

questionnaire being the primary source of its shortcomings. Due to a lack of control over passive smoking and other factors, smoking status was only assessed at the time of patient recruitment. Furthermore, it does not account for those who quit smoking or those who restart after a period of time. False and covert reporting cannot be completely ruled out either, as smoking data is obtained via the questionnaire. It can be more obvious whether the patient has smoked recently if biochemical indications are employed for verification. Like Serretta et al.'s RCT [22], the sample size was modest, and it only looked at smoking status at the time of diagnosis, ignoring any changes in tobacco usage during follow-up and beyond. Furthermore, a high percentage of patients were lost to follow-up, and the trial lacked rigorous prospective control. In contrast, there are very few e-cigarette users in the Kwan et al.'s report [56], and recall bias regarding smoking behavior in participant self-reports cannot be ruled out. The results solely pertain to the relationship between smoking behavior and short-term (≤ 2 years) risk of relapse and progression; they do not address long-term risk.

Three hundred fifty-four NMIBC patients had a history of smoking, according to a paper by Furberg et al [57]. The key is to employ biochemical markers to determine "people who are smoking" with accuracy, prevent patients from disclosing that they smoke, and prevent misreporting by non-smokers who may be exposed to nicotine from other sources. In addition to having small sample numbers, brief follow-up periods, and succumbing to the traps of qualitative analysis, the study shows no correlation between smoking exposure and the likelihood of relapse. It is thought that when the sample size is large enough, the follow-up period is long enough, and the cumulative smoking exposure is the same in quitters and current smokers, stratified investigations of smoking cessation time will produce more acceptable results. As only 14% of the NMIBC group stopped smoking after receiving a diagnosis, there was sampling bias, and the findings in the van Osch et al.'s research were not representative [58]. Furthermore, the study did not standardize postoperative adjuvant treatment or tumor characteristics (stage, grade, size, and number of tumors). Lastly, the data revealed that almost one-third of those who had quit were certain to start smoking again after receiving a diagnosis. This just serves to emphasize the importance of ambulatory monitoring and long-term follow-up. As shown by Serretta et al., quitting smoking at the time of diagnosis did not significantly lower the risk of tumor recurrence [59]. It makes sense to restrict the study participants to quitting and long-term smokers to examine the impact of quitting on relapse and the advancement of NMIBC. The sample size is too small to support a stratified investigation, and the conclusions' application is constrained.

Systematic reviews and meta-analysis

Smoking promoted the recurrence and progression of NMIBC (the difference was statistically significant)

In a meta-analysis involving 7885 patients with NMIBC, Ślusarczyk et al. found that smokers (current or past) had a greater risk of relapse [60]. (95% CI 1.34–2.09; $p < 0.0001$). Relapse risk was 1.24 times greater in current smokers than in former smokers (OR = 1.24; 95% CI 1.02–1.50; $p = 0.03$), according to a subgroup analysis of 2967 patients. When compared to never smokers, smokers had a greater chance of relapse (HR = 1.31; 95% CI 1.15–1.48; $p < 0.0001$) and progression (HR = 1.18; 95% CI 1.08–1.29; $p < 0.001$), according to a meta-analysis of survival ratios. The risk of UCB increases by 2–4 times for current smokers; however, this risk can be lowered by giving up smoking. There was little correlation seen between smoking and other outcomes in patients with TURBT and RC, and smoking status, exposure, and quitting had a substantial effect on disease recurrence for patients undergoing TURBT, according to Rink et al.'s report [61]. Current smokers had a higher chance of a local recurrence of NMIBC, according to Van Osch et al. (HR 1.27, 95% CI 1.09–1.46) [62]. Comparable to the findings of Hou et al.'s report, smoking status had a positive correlation with the chance of bladder cancer recurrence (SRRE = 1.23; 95% CI 1.05–1.45) as well as history (SRRE = 1.22; 95% CI 1.09–1.37) [63]. Still, there was no statistically significant correlation between smoking status (SRRE = 1.11; 95% CI 0.71–1.75) or history (SRRE = 1.16; 95% CI 0.92–1.46) and the risk of BCa development (Table 3).

Smoking promotes the recurrence and progression of NMIBC (no statistically significant difference)

Smoking lifelong or persistently is suggestive evidence of moderate risk factors for relapse, which can be positively modified by quitting. This was found in a systematic review by Aveyard et al [15]. Still, the majority of the research's findings lack statistical significance, and methodological flaws make the evidence basis flimsy. Caini et al. conducted an analysis of the nine included studies and found no statistically significant difference between the quitters' and the continuing smokers' risk of relapse (SHR 0.99, 95% CI 0.61–1.61) [64] (Table 3).

Result and deficiency

The six aforementioned systematic reviews and meta-analyses shared the same issue, and the original research—mostly retrospective cohort studies—limited the meta-analysis's quality [15, 60–64]. The shortcomings of retrospective research are unavoidable for these publications, and by

Table 3 Effects of smoking on the recurrence and progression of NMIBC: systematic reviews and meta-analysis

Author	Research type	Smoking status	Smoking exposure	Recurrence and Progression	Key findings
Ślusarczyk [60]	A systematic review and meta-analysis of 64 studies (6 Prospective cohort studies and 58 retrospective cohort studies) were included	Non-smokers, current smokers, and former smokers	NA	Recurrence and progression	Smokers (current or former smokers) had a higher risk of relapse (OR = 1.68; 95% CI: 1.34–2.09; $p < 0.0001$). Current smokers had a 1.24 higher risk of relapse (OR = 1.24; 95%CI 1.02–1.50; $p = 0.03$). Relapse in smokers (HR = 1.31; 95% CI 1.15–1.48; $p < 0.0001$) and progress (HR = 1.18; 95% CI 1.08–1.29; $p < 0.001$) have a have a higher risk.
Aveyard [15]	A systematic review of 15 studies	Former smokers and current smokers	NA	Recurrence	Lifelong smoking or continuous smoking is suggestive evidence of a moderate risk factor for death and recurrence, which can be positively impacted by stopping smoking. Nevertheless, the majority of the studies' findings were not statistically significant, and methodological flaws made the evidence foundation poor.
Caini [64]	A systematic review and meta-analysis of nine studies were included	Ex-smokers and current smokers	NA	Recurrence	The risk of relapse appeared to be no lower in former smokers than in continuing smokers (SHR 0.99, 95% CI 0.61–1.61).
Rink [61]	A systematic review and meta-analysis of 34 studies were included	Non-smokers, current smokers, and former smokers	Number of cigarettes smoked per day, and smoking years	Recurrence	Current smoking increases the incidence of UCB by two to four times, while quitting reduces this risk. For patients receiving TURBT, smoking status, exposure, and cessation had a significant impact on disease recurrence.
van Osch [62]	A systematic review and meta-analysis of 24 studies were included	Non-smokers, current smokers, and former smokers	Number of cigarettes smoked per day, and smoking years	Recurrence	Current smokers at diagnosis had an increased risk of local recurrence of NMIBC (HR 1.27, 95%CI 1.09–1.46), and smokers with MIBC had an increased risk of death from bladder cancer (HR 1.23, 95%CI 1.02–1.44).

Table 3 (continued)

Author	Research type	Smoking status	Smoking exposure	Recurrence and Progression	Key findings
Hou [63]	A systematic review and meta-analysis of 15 studies were included	Non-smokers, current smokers, and former smokers	Number of cigarettes smoked per day, and smoking years	Recurrence	Current smoking and risk of bladder cancer recurrence (SRRE = 1.23; 95%CI 1.05–1.45) was positively correlated. Furthermore, recurrence of bladder cancer was favorably connected with prior smoking (SRRE= 1.22; 95% CI, 1.09–1.37). The risk of bladder cancer development did not significantly correlate with either the present (95%CI, 0.71–1.75) or prior (95%CI 0.92–1.46) smokers. It was, however, equivalent to the former group.

accounting for factors like real smoking, postoperative treatment methods, tumor characteristics, demographic characteristics, and quality of repeat TURBT, they may even exacerbate this shortcoming. The inclusion of 7885 patients in the Ślusarczyk et al.'s analysis allowed for the amplification and statistical differentiation of the differences between non-smokers and smokers (including ex-smokers and current smokers) [60]. However, we advise against drawing straight parallels between quitting and non-smokers. This simply explains why quitting smoking increases the chance of relapsing; it does not explain why quitting smoking alone or in combination with other factors contributes less to recurrence. There are also a lot of important restrictions on the study. Six prospective cohort studies were included out of 64 original investigations. Only two of these six prospective trials, nevertheless, examined the impact of smoking on the development and recurrence of NMIBC. The remaining investigations included smoking as a possible confounder in univariate or multivariate analysis; however, since smoking status was not the primary focus of these studies, reporting bias was unavoidably present. Inconsistencies also existed in baseline attributes such as patient age, tumor stratification, and postoperative adjuvant therapy. Similar issues plagued the other five meta-analyses [15, 61–64]. Here, we will not go through them one by one.

Discussion

In terms of mechanisms, single nucleotide polymorphisms in cytochrome P450 reductase, N-acetyltransferase, glutathione S-transferase, genes linked to inflammation, STK12 genes, and DNA-repair genes, as well as DNA damage brought on by tobacco carcinogens, are all signific`ant contributors to the development of cancer [65–68]. UCB patients' prognosis and HPV DNA presence are significantly correlated, according to recent studies [69]. Tumor recurrence was reported by 47.3% of 19 HPV-positive patients ($n=9$) and 36.8% of 38 HPV-negative patients ($n=14$), with no significant differences in age, follow-up period, smoking status, or tumor grade ($p=0.445$). During the 2-year follow-up period, there was a correlation found between the presence of HPV DNA and an increased susceptibility to relapse. According to a number of studies [70–72], lower e-cadherin expression encourages BCa metastasis and progression and is linked to a poor prognosis. Restoring E-cadherin expression can stop tumor invasion, metastasis, and progression. Li et al. conducted more research and discovered that the unique dsRNA-mediated up-regulation of E-cadherin expression impeded the expansion and metastasis of BCa cells by blocking the genes that target β-catenin/TCF [73]. Furthermore, a stronger correlation was found between decreased BCa outcomes and elevated miR-155 levels [74, 75]. Lu et al.'s

additional research revealed that the expression of miR-155 varied between RT4 and T24 BCa cells [76]. Via the intercellular transfer of TNTs, miR-155 can activate the Deptor-mTOR signaling pathway, thereby facilitating the invasion and growth of BCa cells. Numerous signaling pathways, including the MAPK/ERK, PI3K/Akt, and JAK/STAT pathways, have been shown to be activated by nicotine through nicotinic acetylcholine receptors. These pathways are linked to tumor development and acquired treatment resistance in addition to tumor formation [77–79]. The PI3K/Akt/mTOR pathway may be activated by nicotine exposure in vitro and in vivo in research to promote tumor cell proliferation. Conversely, blocking this system may decrease BCa cell line T24 viability [80]. These initial results offer foundational ideas for mitigating nicotine exposure and decreasing the aggressiveness of bladder cancerous growths.

According to the number of included study populations and references, the majority of research (14 references) revealed that smoking significantly accelerated the progression and recurrence of NMIBC in patients [12, 13, 22, 47–52, 56, 60–63]. Smoking had no effect on the recurrence or advancement of NMIBC in patients, according to less than half of the investigations (10 papers) [11, 15, 23, 53–55, 57–59, 64]. Meta-analyses utilizing randomized controlled studies or prospective cohort studies as the primary research studies offer the strongest level of evidence. But unfortunately, no such evidence is available. Certain meta-analyses that rely on retrospective cohort studies [61, 62], prospective cohort studies [12, 22, 56], and retrospective cohort studies [13, 47, 49, 51] still hold some guiding significance. Almost all of the research also supports stopping smoking, which enhances quality of life in relation to health. The pathological types of BCa mentioned in the above 24 articles are all urothelial carcinoma. While there are gender disparities in bladder cancer incidence, men are more likely than women to develop BCa. But none of the 24 publications mentioned above examined how smoking affected NMIBC patients' progression and recurrence from a gender standpoint. Gender did not distinguish between current smokers, former smokers, or never smokers. One of the publications provided a plausible explanation [49]: it was not possible to segment the study by gender because the prevalence of smoking among women during the same period was just 4%. Therefore, we cannot know whether there is a gender difference in the "effect of smoking on the recurrence and progression of non-muscle-invasive bladder cancer".

These investigations were constrained by retrospective cohort studies, unreliable exposure evaluations, and small sample sizes. Due to their small sample size and short follow-up period, prospective cohort studies are few. Of the twenty-four articles, a large number focused on the relapse and progression outcomes of non-smokers, ex-smokers, and chronic smokers, falling into the trap of qualitative analysis

[11, 23, 53–55]. There are not many literary works that have managed to escape the confines of qualitative analysis and examine smoking exposure as well as status. The impact of smoking on the development and recurrence of NMIBC was examined by contrasting never-smokers with current smokers. Cumulative smoking exposure was the only variable. The study should only include smokers who are currently active to better examine the impact of smoking intensity and duration on relapse and progression. To examine the impact of quitting on the recurrence and progression of NMIBC, current and former smokers were matched. When cumulative smoking exposure was equal, the effects of quitting on relapse and progression were evaluated. Former smokers should be the only ones included in the study to more thoroughly examine the impact of smoking intensity and time prior to quitting on relapse and progression. Comparing never-smokers to ex-smokers is inappropriate since there are two variables to consider: smoking and quitting. The sole variable is not smoking or stopping. It is also not appropriate to compare smokers (both past and present) with those who have never smoked. Releasing oneself from smoking reduces the harmful consequences of prior smoking to some extent, even though smokers are still exposed to smoking. The people who smoke now are most affected by smoking, followed by those who have smoked in the past, and lastly, those who have never smoked. A former smoker's cumulative smoking exposure is not always smaller than a smoker's present exposure, though when looking at it quantitatively.

Compared to other tobacco-related diseases, bladder cancer is not as well known to the general public [81–83]. When BCa was first discovered in about 30% of patients, they were still heavy smokers [84]. Roughly 40% of smokers continue to smoke while receiving treatment for BCa [22]. Furthermore, few urologists provide their patients with any therapies to assist in quitting [17, 83] because they may not think that quitting smoking is crucial to the clinical care of BCa [85]. A lack of clinical proof could be the cause of this [85]. Positively, with medical guidance, most individuals with BCa are willing to give up smoking [86]. According to a prospective experiment, patients' rates of quitting smoking increased dramatically (from 2.6% to 12.1%) after receiving a smoking cessation intervention for as little as five minutes. Clearly, higher rates of smoking cessation may result from improved clinician and patient understanding of the value of quitting smoking in the management of illness [87].

Prospective cohort studies (or RCTs) are better equipped to address the limitations of retrospective cohort studies, including an inability to account for genuine smoking status, postoperative treatment, tumor features, population factors, and repeated TURBT and TURBT quality. Among them [57], recollection bias and purposeful concealment can be significantly mitigated by employing biochemical markers to reliably identify "people who are smoking." Furthermore,

dynamic monitoring and follow-up over an extended period of time are crucial. Smokers who have altered over time can be identified through dynamic monitoring. Excessive overlap between present and previous smokers was more likely to occur during shorter follow-up periods. The entire scope of disparities between present and previous smokers will be revealed by long-term follow-up [22, 63]. The following factors must be carefully controlled: smoking status must be authentic and reliable (questionnaire survey combined with biochemical verification); demographic characteristics (age, gender); tumor characteristics (stage, grade, tumor size, tumor number); and postoperative treatment plan (whether perfusion therapy, chemotherapy drug infusion therapy, or repeated surgery). Stratified studies must be conducted to clearly understand the effects of smoking cessation years, smoking time, and smoking exposure on relapse and progression of NMIBC patients. Large samples are the basic and necessary conditions for completing stratified analysis.

We should increase public awareness of smoking-related hazards and focus on improving the prognosis of other tobacco-related systemic diseases and improving quality of life, even though the conclusion that smoking promotes relapse and progression in patients with NMIBC is not supported by high-quality, large-sample prospective cohort studies (or randomized controlled studies). Simultaneously, there is an increased focus on deterring nonsmokers from starting to smoke as well as helping current smokers to give up as soon as feasible [57].

Conclusion

When combined with the information now available on NMIBC, smoking is widely acknowledged to have a negative impact on patient outcomes. It is also known to accelerate the progression and recurrence of BCa. Reducing tobacco use lowers the risk of cardiovascular events, all-cause mortality, and second primary malignancies while also improving health-related quality of life and making procedures safer. Encouragement and assistance in quitting smoking should be provided to all patients who smoke. Large-scale, high-quality Prospective cohort study (or RCT) evidence is desperately needed to support the weak evidence that smoking causes the recurrence and progression of BCa in clinical practice. These limitations stem from the study type, sample size, and design. This has substantial clinical implications for urologists' scientific cognition, increasing smoking cessation counseling, bolstering smoking cessation publicity, and lessening patient financial load while enhancing patient prognosis.

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Data availability Given that no new data were created or analyzed for this study, data sharing is not applicable to this publication.

Declarations

Conflicts of interest No conflicts of interest have been disclosed by the authors.

Ethical approval Ethical approval does not apply because this work is not research involving humans and/or animals.

Informed consent Not applicable.

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