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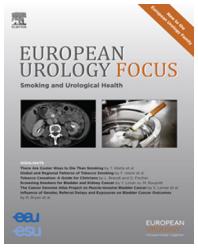

Review – Bladder Cancer

Smoking and Bladder Cancer: A Systematic Review of Risk and Outcomes

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Abstract

Context: Cigarette smoking is an established risk factor for urothelial carcinoma.
Objective: To elucidate the association between pretreatment smoking status, cumulative exposure, and time since smoking cessation and the development of and outcomes for urothelial carcinoma of the bladder (UCB) in patients treated with transurethral resection of the bladder (TURBT) or radical cystectomy (RC).
Evidence acquisition: A literature search was performed in September 2014 using the PubMed and Scopus databases limited to articles published in English since 1990. Eight contemporary studies on smoking and UBC development and 26 studies on smoking and UBC prognosis met the inclusion criteria.
Evidence synthesis: Current cigarette smoking increases the risk of UCB incidence by two to fourfold, while smoking cessation attenuates this risk. Smoking status, exposure, and cessation have an evident impact on disease recurrence for patients who undergo TURBT, with weaker associations between smoking and other endpoints for TURBT and RC patients.
Conclusion: Retrospective evidence suggests that smoking markedly increases UCB risk and may lead to unfavorable outcomes for patients who already have UCB; smoking cessation can attenuate these undesirable effects.
Patient summary: Current evidence proves that cigarette smoking is an established risk factor for the development of urothelial carcinoma of the bladder (UCB). There is a growing body of evidence that smoking negatively affects outcomes for UCB patients treated with transurethral resection and/or radical cystectomy, although not uniformly. Long-term smoking cessation seems to mitigate the detrimental effects of smoking in non–muscle-invasive and muscle-invasive bladder cancer.

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1. Introduction

Urothelial carcinoma of the bladder (UCB) is the sixth most common cancer in both genders, with an estimated 72 570 new cases and 15 210 deaths in the USA in 2013 [1], representing a significant burden of morbidity and mortality. Approximately three-quarters of patients are initially diagnosed with non–muscle-invasive bladder cancer (NMIBC)

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and are thus eligible for bladder-preserving treatment including transurethral resection of the bladder (TURBT) with or without intravesical therapy [2]. By contrast, approximately 30% of patients have muscle-invasive or locally advanced UCB at diagnosis [3], and radical cystectomy (RC) with bilateral lymphadenectomy with or without perioperative systemic chemotherapy is the gold standard treatment for these patients [4].

Despite clear evidence that tobacco smoke contains over 60 carcinogens, causes at least 18 types of cancer, and is the second leading risk factor causing death, >30% of adults in the Western world are still current or former smokers [5–7]. There is convincing evidence that cigarette smoking is the best-established and most important risk factor for the development of UCB [8,9]. The risk of UCB development is inversely associated with age at first exposure and cessation of cigarette smoking [9]. According to current smoking patterns, a global average of approximately 50% of young men and 10% of young women are smokers and only relatively few quit [10]. As these young smokers reach middle and old age, the effects of smoking will represent a future burden for all health care providers including urologists, as UCB is generally a disease of the elderly [11].

UCB has the highest prevalence among all urinary tract malignancies because of moderate progression rates and long-term survival in many patients [8]; nevertheless, UCB screening is not performed, mainly because of the low overall incidence [12]. However, it is important to acknowledge that UCB is the most expensive cancer and has the highest lifetime treatment cost per patient among all cancers [13]. The necessity for long-term monitoring of UCB patients has steadily increased the health economic burden for decades. Together with long-term disease-related psychological effects, the economic burden of UCB surveillance and treatment underscores the urgent need for a better understanding of UCB risk factors and their impact on the natural history of the disease.

It has been suggested that smoking not only promotes carcinogenesis but is also associated with tumor behavior. However, the impact of smoking on the course of UCB disease and outcomes remains poorly understood and controversial. There is evidence from different smoking-related malignancies that continuing smoking after diagnosis negatively affects oncologic outcomes [14]. Previous studies investigating the effects of smoking on disease outcomes and prognosis face important methodological barriers, and it is important to realize that smoking is not just smoking [15]. To quantify cumulative cigarette smoking exposure, the medical convention has favored pack-years (average number of packs smoked per day multiplied by smoking duration in years). This measure assumes that duration and intensity (packs per day) have equivalent effects, but growing evidence suggests that this is not the case. In addition, long-term smoking cessation decreases the risk of cardiovascular and lung disease and the likelihood of developing various malignancies [16]. However, whether smoking cessation and time since cessation beneficially influence oncologic outcomes in UCB remains inconclusive.

Therefore, a better understanding of smoking-related biology in UCB development and the role of smoking in UCB prognosis may significantly influence clinical management strategies and thus health costs. In this systematic review we summarize evidence from the most recent articles regarding the effects of smoking and smoking cessation on UCB development and oncologic outcomes for patients with NMIBC and MIBC.

2. Evidence acquisition

2.1. Search strategy

J.J.C. conducted a literature search in September 2014 using the PubMed and Scopus databases. The following search was performed: (smok* OR tobacco OR cig* OR "smoking cessation") AND (cancer OR carcinoma OR neoplas* OR tumor) AND (bladder OR urothelial OR "transitional cell") AND ("risk factor" OR recur* OR progression OR survival OR death OR mortality OR prognos* OR outcome). Filters were applied to capture items published in English on or after January 1, 1990.

2.2. Study eligibility

Our procedure for including studies in this review is outlined in Figure 1, consistent with Preferred Reporting Items for Systematic Reviews and Meta-analyses [17]. M.R. and J.J.C. read all resulting abstracts and full-text articles in depth. All authors agreed that the articles selected for this review met the inclusion criteria dictated by the patient population, intervention/exposure, comparison, outcome, and study design (PICOS) approach. A record was considered relevant to this review if it assessed the following: adult men and women treated with surgery for UCB; significant smoking history or smoking exposure compared with lesser smoking history or smoking exposure or smoking cessation; and diagnosis of UCB and patient outcomes, including disease recurrence or progression and cancer-specific and any-cause mortality. We accepted all study designs except for case reports. Meeting abstracts, editorials, and commentaries on articles were not accepted, nor were review articles or meta-analyses.

In an effort to provide the most recent data available, only studies published in 2011 or later were considered for associations between smoking and UCB risk (Fig. 1). In addition, we required that at least 100 patients were present in both the case and control groups.

We considered all items published in 1990 or later for associations between smoking and outcomes for UCB (Fig. 1). We divided studies into two groups according to the intervention performed (TURBT or RC). Cohorts for which both TURBT and RC outcomes were reported were excluded because these cohorts were deemed too heterogeneous for our analysis. We also required that the majority of the patients had urothelial carcinoma histology and that there were at least 10 patients in each smoking status or exposure group.

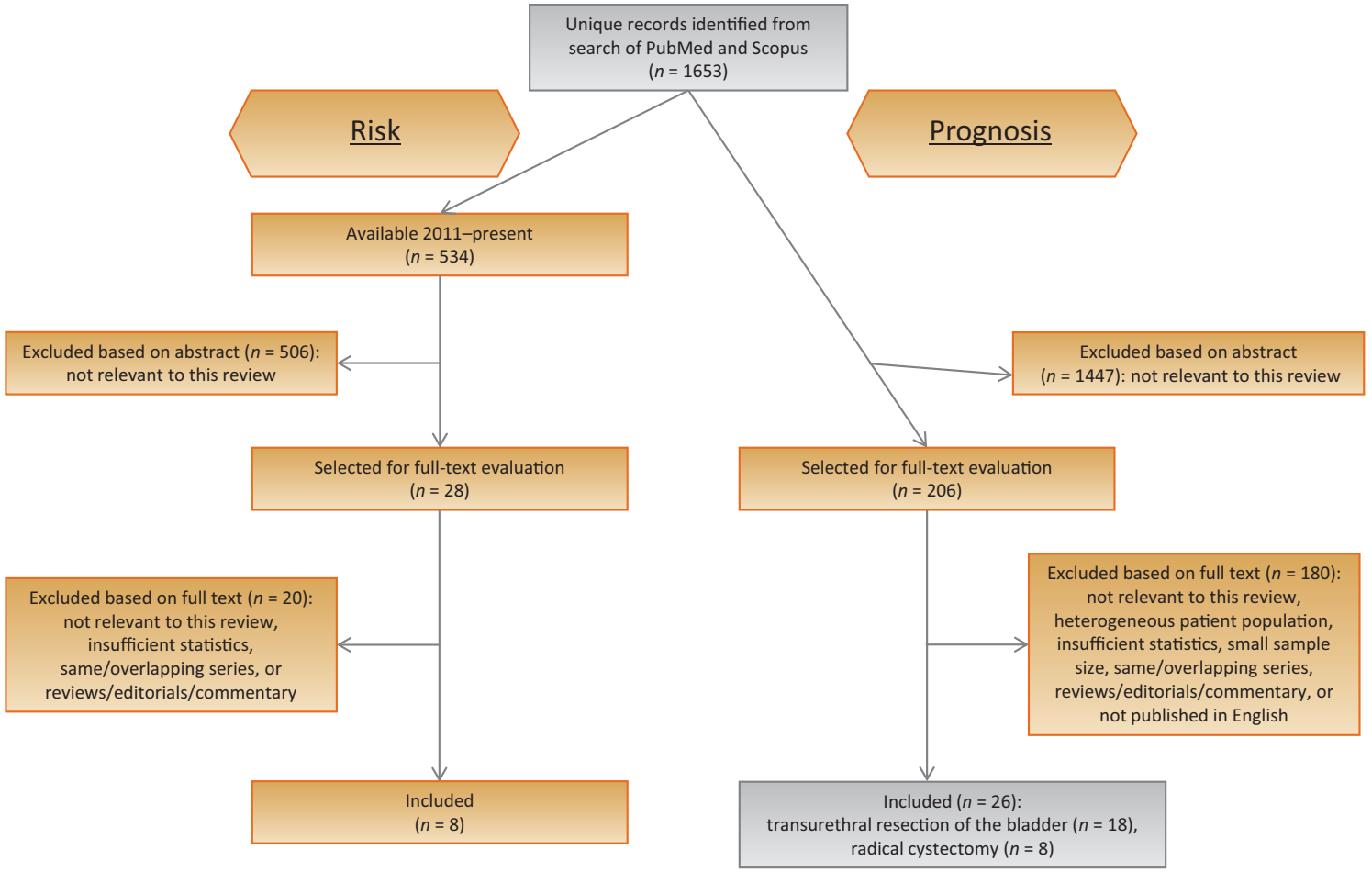

Fig. 1 – Outline of the search strategy and study inclusion process for this systematic review.

Studies reporting associations between smoking cessation and disease outcomes were also subjected to the aforementioned criteria. In addition, we required that the time period over which smoking cessation took place was clearly delineated and that the comparator group contained patients who were smoking at the time of diagnosis.

2.3. Data extraction

J.J.C. tabulated the data from all the studies included and M.R. reviewed the tables for accuracy. For studies reporting associations between smoking and UCB risk, we required that odds ratios (ORs) were available with 95% confidence intervals (CIs). When not available, ORs were calculated if the data permitted this. For associations between smoking and clinical outcomes, we recorded p values (or 95% CIs if p values were not provided), along with hazard ratios (HRs) or ORs if they were available. If both multivariate and univariate analyses were performed for the same smoking-endpoint association, we recorded the result of the multivariate analysis. Statistical significance was defined as $p < 0.05$.

3. Evidence synthesis

3.1. Bladder cancer risk

We estimate that several hundred case-control and cohort studies have been conducted to estimate the risk of UCB attributable to smoking. An analysis performed in 2011 of 467 528 men and women found that former and current smokers had two- and fourfold increases, respectively, in UCB risk relative to never smokers [18]. The population risk of bladder cancer attributable to smoking was approximately 50% for both men and women.

This review summarizes the impact of smoking on bladder cancer risk in studies published since 2011. Among the eight case-control studies selected (Table 1) [19–26], UCB risk was two- to fourfold higher for current smokers, and up to threefold higher for former smokers. Risk estimates were similar for men and women across studies. One study found that smoking was more strongly associated with the development of MIBC than with NMIBC [22]. While smoking cessation attenuates UCB risk, former smokers are still approximately twice as likely to develop the disease 20 yr after quitting [24].

Overall, the most current risk estimates are consistent with those of Freedman et al [18] from 2011. Interestingly, changes in the composition of cigarette smoke that might be more likely to induce bladder carcinogenesis could explain the nearly unchanged incidence in UCB despite the decreased prevalence of smoking. Although the molecular mechanisms behind bladder carcinogenesis remain incompletely elucidated, several have been proposed [27–29]. In addition, investigating specific genetic susceptibilities may help in understanding smoking-related risk profiles for individual patients [30].

It is important to note that case-control studies such as those reported here are limited by their retrospective nature and demographic and clinical differences often unaccounted for between case and control populations. However, they are often adequate for obtaining risk estimates, especially in light of the high cost of performing a prospective cohort study.

Table 1 – Selected studies reporting associations of smoking and risk of urothelial carcinoma of the bladder

Study	Years	Cases (n)	Controls (n)	Mean or median age (years)	Male (%)	Smoking category*	Estimate
Alguacil et al. (2011)	1998-2001	712	611	NR	89	Ever	OR=2.4†
						Former	OR=1.8†
						Current	OR=3.7†
Jiang et al. (2012)‡	1987-1996	1586	725	56	78	Ever	OR=2.2 (1.8-2.8)
						Former	OR=1.7 (1.3-2.1)
						Current	OR=3.2 (2.5-4.1)
Zheng et al. (2012)‡	2006-2010	765	1651	58	100	Ever	OR=2.0†
						Former	OR=1.2 (0.9-1.7)
						Current	OR=2.1 (1.7-2.6)
Ferreccio et al. (2013)	2007-2010	232	640	NR	69	Ever	OR=1.6 (1.1-2.2)
Erdurak et al. (2014)‡	2011	173	282	68§; 65‖	NR	Ever	OR=3.2†
						Former	OR=3.3 (1.8-5.8)
						Current	OR=3.0†
Moura et al. (2014)	1998-2011	4312	26971	NR	55‖	Ever (male)	OR=3.0 (2.8-3.2)
						Ever (female)	OR=3.0 (2.6-3.4)
Welty et al. (2014)‡	2000-2008	378	76055	NR	48	Ever	OR=2.8†
						Former	HR=2.0 (1.6-2.6)
						Current	HR=3.8 (2.7-5.4)
Wu et al. (2014)	2002-2009	261	672	61	67	Ever	OR=2.3 (1.6-3.3)

NR=not reported; OR=odds ratio; HR=hazard ratio.
* All risk estimates are relative to never smokers.
† Calculated based on available raw data.
‡ Refer to full text for smoking quantity and duration data.
§ Applies to cases only.
‖ Applies to controls only.

3.2. Bladder cancer outcomes

3.2.1. Transurethral resection of the bladder

For patients treated with TURBT, smoking status and cumulative lifetime smoking exposure seem to influence disease prognosis (Table 2). The majority of studies (10 of 16) found that active/current cigarette smoking, as well as high lifetime exposure, significantly increase the risk of disease recurrence [31–46]. There is only moderate evidence that smoking increases the risk of disease progression in NMIBC (4 of 11 studies) [33,35,37–39,41–43,45,47,48]. In addition, there is also no conclusive evidence of an association between smoking and cancer-specific mortality or any-cause mortality in NMIBC [42,43,45]. The evidence for these three endpoints, however, is obviously compromised by a lack of data and overall low mortality rates for patients with NMIBC. The same is true regarding the gender-specific effect of smoking on NMIBC outcomes [49]. The findings are contradictory across studies and thus no final conclusions can be drawn. In addition, findings regarding the influence of smoking cessation on outcomes in NMIBC are partly conflicting, but the evidence for a reduction in recurrence rates is strongest (Table 4, 4 of 6 studies) [33,34,37,40,42,43]. In addition, there is some evidence that smoking reduces the efficiency of intravesical chemotherapy and immunotherapy [31,35,36,40,44,45,50]. This finding seems reasonable considering the immunomodulatory effects of tobacco smoke.

Although the current evidence represents an improvement because of emerging interest in elucidating the associations between smoking and NMIBC outcomes, several study-related and general limitations need to be overcome in future research. In general, NMIBC is a complex and heterogeneous disease: while some patients experience early disease recurrence or even disease progression, others remain free of their disease for a long time if not forever [8]. However, subset analyses of particular NMIBC risk groups (eg, intermediate vs high risk, low-grade vs high-grade tumors) are currently lacking. Moreover, the impact of smoking according to different treatment modalities (eg, white light vs photodynamic diagnosis for TURBT guidance, repeat TURBT) remains unexamined to the best of our knowledge.

For risk stratification and patient counseling, two established models are frequently used, the risk tables of the European Organization for Research and Treatment of Cancer and Club Urologico Espanol de Tratamiento Oncologico (Spanish Urological Oncology Group) [2]. Recently published studies have challenged the accuracy and clinical utility of these models because of insufficient discrimination [51]. In fact, both models adjust for several established risk factors, but do not adjust for the impact of the best-established individually modifiable risk factor, which may improve outcome predictions.

Finally, UCB carcinogenesis is a complex process affected by several inherent genetic and biologic factors, as well as geographic, environmental, occupational, and social behavioral elements [52]. The majority of current studies only controlled for smoking as a sole risk factor, and studies adjusting for combinations of risk factors are warranted.

3.2.2. Radical cystectomy

There is some evidence that smoking impacts disease prognosis in UCB patients treated with RC (Table 3), although this effect was less apparent compared to patients treated with TURBT. Overall, two of eight studies found that cigarette smoking was an independent predictor of disease recurrence, cancer-specific mortality, or overall survival [53–60]. Again, current smoking status and escalating lifetime smoking exposure were inversely associated with outcomes in these studies.

The highest level of evidence is obtained from prospective, randomized controlled studies, but the results reported here are from retrospective studies with all the inherent limitations that may limit the evidence base. Of particular importance for research on smoking is the fact that smoking status and exposure are mostly self-reported and are therefore subject to recall bias. Validated questionnaires to assess smoking in patients with cancer at different points during the disease course are still being developed [61]. In addition, if current smokers report themselves as former smokers, associations between smoking and outcomes would be biased toward the null, especially if such patients could not successfully quit smoking following diagnosis. Biochemical verification of smoking status may be a goal for future investigations.

The influence of smoking cessation on outcomes for UCB patients after RC remains undetermined (Table 4). We found only one study addressing this association, and it showed that quitting smoking reduced the risk of disease recurrence, cancer-specific mortality, and any-cause mortality [58]. Since there is some evidence that smoking influences the course of UCB, urologists should not only counsel patients regarding the detrimental effects of smoking but also assist in their smoking cessation attempts [62,63]. The association between smoking and UCB is not as well known as that for lung cancer [64]. For many patients, cancer diagnosis represents a teachable moment to motivate them to successfully quit smoking. UCB patients are often willing to quit smoking with the help of their physicians [65]. Appropriate patient education and brief physician meetings may increase compliance to ultimately cease smoking, improve outcomes, and enhance quality of life, as current smokers report increased fear of disease recurrence and psychological distress compared to nonsmokers [66]. However, too few patients are currently offered any intervention to aid in cessation by their urologists [64,67].

We also found contradictory evidence regarding a gender-specific effect of smoking in these patients. Interestingly, previous studies reported gender-specific differences in MIBC outcomes: women presented with more aggressive tumor biology and unfavorable sequelae [68]. Thus, this issue should be the subject of future investigations to clarify the effect of smoking on these variations.

As with NMIBC, research regarding the effects of smoking in MIBC needs to continue to improve our understanding and answer many questions. For example,

Table 2 – Selected studies reporting associations of smoking and outcomes of patients with urothelial carcinoma of the bladder treated with transurethral resection of the bladder

Study	Study and patient characteristics							Outcomes							
								Disease recurrence		Disease progression		Cancer-specific mortality		Any-cause mortality	
	Years	Sample size (*n*)	Mean or median age (years)	Pathological stage (%)	Pathological grade (%)	Additional intervention (%)	Mean or median follow-up (months)	Smoking status	Smoking exposure	Smoking status	Smoking exposure	Smoking status	Smoking exposure	Smoking status	Smoking exposure
Allard et al. (1995)	1990-1992	368	65.1	Ta 78.8; T1 21.2	G1 34.2; G2 53.8; G3 12.0	Re-TUR NR; BCG 17.4; Chemo 2.2	23.7	HR=1.28 (0.82-1.98);* HR=1.45 (0.94-2.24)†	-	-	-	-	-	-	-
Cheng et al. (1999)	1987-1992	83	72	T1 100	LG 33.7; HG 66.3	Re-TUR NR; BCG 13.3; Chemo 19.3; Radiation 1.2	64.8	-	-	*p*=0.22‡	-	-	-	-	-
Fleshner et al. (1999)	1985-1995	286	61.2	Ta 52.4; Tis 16.8; T1 30.8	G1 33.6; G2 31.1; G3 35.3	Re-TUR 100; BCG 22.7; Chemo NR	57.3	HR=0.99, *p*=0.89;§ **HR=1.40, *p*=0.03**‖	-	-	-	-	-	-	-
Chen et al. (2007)	1997-2005	265	67	Ta 62.4; T1 37.6	LG 72.5; HG 27.5	Re-TUR NR; BCG 18.9; Chemo 57.7	38	**HR=2.2, *p*=0.03**;¶ HR=1.4, *p*=0.35;** **HR=2.2, *p*=0.01**††	HR=1.01, *p*=0.98;‡‡ HR=1.5, *p*=0.27;§§ **HR=2.1, *p*=0.02**‖‖	*p*=0.43;‖ *p*=0.29;† **p=0.02**††	-	-	-	-	-
Gee et al. (2009)	1991-2003	43	67	NR	NR	Re-TUR NR; BCG 100; Chemo NR	NR	HR=3.20, *p*=0.05;¶¶ **HR=0.27, *p*=0.03**‖	-	-	-	-	-	-	-
Gangawar et al. (2010)	2006-2008	135	57.1	NR	G1 50.4; G2/G3 49.6	Re-TUR NR; BCG 54.8; Chemo 0.0	14	**HR=1.86, *p*=0.02**¶¶	-	HR=1.96, *p*=0.39¶¶	-	-	-	-	-
Hwang et al. (2011)	2000-2010	251	67	Ta 63.7; T1 36.3	PUNLMP 5.6; LG 62.5; HG 31.9	Re-TUR NR; BCG 50.1; Chemo 14.3	34	**HR=1.63, *p*=0.02**¶¶	-	*p*=0.21¶¶	-	-	-	-	-
Lammers et al. (2011)	1998-2004	718	66.5	Ta 78.7; T1 21.3	G1 42.1; G2 47.0; G3 10.9;	Re-TUR NR; BCG NR; Chemo 100	30	**HR=1.47, *p*=0.048**¶¶	*p*=0.30;*** *p*=0.25;††† *p*=0.06‡‡‡	-	-	-	-	-	-
Sfakianos et al. (2011)	1994-2008	623	76	Ta 35.2; Tis 30.3; T1 34.5	LG 9.6; HG 90.4	Re-TUR 100; BCG 100; Chemo NR	80.9	HR=1.05, *p*=0.68;¶¶ HR=1.05, *p*=0.65;* HR=1.04, *p*=0.81†	-	HR=1.02, *p*=0.93;¶¶ HR=1.00, *p*=0.99;* HR=1.16, *p*=0.61†	-	HR=1.14, *p*=0.49;¶¶ HR=1.20, *p*=0.34;* HR=1.03, *p*=0.91†	-	HR=1.15, *p*=0.61;¶¶ HR=1.14, *p*=0.63;* HR=1.27, *p*=0.49†	-
Ajili et al. (2012)	2000-2007	112	63.9	Ta 60.7; T1 39.3	G1 39.3; G2 43.8; G3 17.0	Re-TUR NR; BCG 100; Chemo NR	NR	HR=0.49, *p*=0.06¶¶	-	-	-	-	-	-	-
Rink et al. (2012)	1987-2007	390	67	Ta 67.9; Tis 1.5; T1 30.5	G1 36.9; G2 28.7; G3 34.4	Re-TUR NR; BCG 15.4; Chemo 3.3	66	*p*=0.5;* *p*=0.4;† *p*=0.7‖	**p=0.02**;§§§ **p<0.001**;‖‖‖ **HR=2.08, p=0.006**;¶¶¶ **HR=4.31, p<0.001******	*p*=0.7;* *p*=0.2;† *p*=0.2‖	**p<0.001**;§§§ **p<0.001**;‖‖‖ **p=0.003**††††	-	-	*p*>0.05* *p*>0.05;‖	-

Segal et al. (2012)	1995-2005	278	72.8	T1 100	HG 100	Re-TUR NR; BCG 35.6; Chemo NR	36	-	-	HR=1.15, p=0.51[¶¶]	-	-	-	-	-
Rink et al. (2013)	1987-2007	2043	67	Ta 61.0; T1 39.0	G1 23.6; G2 33.8; G3 42.6	Re-TUR NR; BCG 16.1; Chemo 3.8	49	HR=1.12 (0.94-1.34);[*] **HR=1.22 (1.01-1.48)**[†]	**HR=0.43 (0.30-0.60)**;[‡‡‡‡] HR=0.91 (0.77-1.07);[§§§§] **HR=0.35 (0.26-0.47)**[‖‖‖‖]	HR=1.29 (0.79-2.09);[*] **HR=2.09 (1.29-3.39)**[†]	**HR=0.12 (0.03-0.44)**;[‡‡‡‡] **HR=0.43 (0.29-0.63)**;[§§§§] **HR=0.05 (0.01-0.19)**[‖‖‖‖]	-	-	HR=1.10 (0.86-1.41);[*] HR=1.12 (0.85-1.47)[†]	HR=0.81 (0.51-1.27);[‡‡‡‡] **HR=0.67 (0.52-0.85)**;[§§§§] **HR=0.54 (0.37-0.80)**[‖‖‖‖]
Serretta et al. (2013)	2002-2003	395	68	Ta 36.5; T1 63.5	G1 35.9; G2 64.1	Re-TUR NR; BCG NR; Chemo 100	48	**HR=1.60, p=0.04**[¶¶]	-	-	-	-	-	-	-
Grotenhuis et al. (2014)	1995-2012	963	64	Ta 70.0; Tis 3.8 T1 26.2	LG 61.8; HG 38.2	Re-TUR NR; BCG 22.0 Chemo 33.0	44	HR=1.06, p=0.68;[¶¶] p=0.47[‡]	p=0.62[***]; p=0.61[†††]	HR=1.85, p=0.25;[¶¶] p=0.54[‡]	p=0.95[***]; p=0.15[†††]	-	-	-	-
Kashif Khan et al. (2014)	2008-2012	64	59.9	NR	NR	Re-TUR NR; BCG 100; Chemo NR	28.4	NS	-	**OR=4.02, p=0.04**[¶¶]	-	-	-	-	-
Rausch et al. (2014)	1996-2006	192	68.3	Ta 76.3; T1 23.7	G1 43.5; G2 50.0; G3 6.5	Re-TUR NR; BCG NR; Chemo NR	80	OR=1.40, p=0.11[¶¶]	-	OR=0.51, p=0.20[¶¶]	-	-	-	-	-
Wyszynski et al. (2014)	1994-2001	726	NR	Ta/T1 93.7; Tis 6.3	LG 73.1; HG 25.9	Re-TUR NR; BCG NR; Chemo NR	67.2	**HR=1.61, p=0.003**;[*] **HR=1.51, p=0.02**[†]	-	-	-	-	-	-	-

G1=grade 1; G2=grade 2; G3=grade 3; re-TUR=repeat transurethral resection of the bladder; NR=not reported; BCG=bacillus Calmette-Guérin; chemo=adjuvant chemotherapy; HR=hazard ratio; LG=low-grade; HG=high-grade; PUNLMP=papillary urothelial neoplasm of low malignant potential; NS=non-significant.

Bold: statistically significant relationship.

[*] Former vs. never smokers.
[†] Current vs. never smokers.
[‡] Current vs. former vs. never smokers.
[§] Quitters vs. former smokers.
[‖] Current vs. former smokers.
[¶] Never smokers vs. quitters.
[**] Former smokers vs. quitters.
[††] Current smokers vs. quitters.
[‡‡] 20-39 vs. 1-19 pack-years.
[§§] 40-59 vs. 1-19 pack-years.
[‖‖] ≥60 vs. 1-19 pack-years.
[¶¶] Smokers vs. non-smokers.
[***] Number of cigarettes per day.
[†††] Number of years of smoking.
[‡‡‡] Number of pack-years.
[§§§] ≥20 vs. <20 cigarettes per day.
[‖‖‖] ≥20 vs. <20 years of smoking.
[¶¶¶] Moderate vs. light short-term smokers.
[****] Heavy long-term (>20 cigarettes per day for >20 years) vs. light short-term (≤20 cigarettes per day for ≤20 years) smokers.
[††††] Heavy long-term vs. moderate (>20 cigarettes per day for ≤20 years or ≤20 cigarettes per day for >20 years) vs. light short-term smokers.
[‡‡‡‡] Heavy short-term (>20 cigarettes per day for ≤20 years) vs. heavy long-term smokers.
[§§§§] Light long-term (≤20 cigarettes per day for >20 years) vs. heavy long-term smokers.
[‖‖‖‖] Light short-term vs. heavy long-term smokers.

Table 3 – Selected studies reporting associations of smoking and outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy

	Study and patient characteristics							Outcomes					
								Disease recurrence		Cancer-specific mortality		Any-cause mortality	
Study	Years	Sample size (*n*)	Mean or median age (years)	Pathological stage (%)	Pathological grade (%)	Additional intervention (%)	Mean or median follow-up (months)	Smoking status	Smoking exposure	Smoking status	Smoking exposure	Smoking status	Smoking exposure
Thrasher et al. (1994)	1969-1990	531	64.5	Ta 5.8; Tis 4.3; T1 31.3; T2 40.1; T3 7.0; T4 11.5	G1/G2 12.4; G3 42.2; G4 45.4	Neoadj NR; Adj NR	126	-	-	p=0.85[*]	-	-	-
Boorjian et al. (2011)	1980-2000	1506	68	T0-T1 30.0; T2 37.7; T3/T4 32.3	NR	Neoadj/ adj 11.0	162	HR=0.97, p=0.87[*]	-	-	-	-	-
Yafi et al. (2011)	1998-2008	2287	68	T0-T2 50.7; T3/T4 49.3	LG 10.1; HG 89.9	Neoadj 3.4; Adj 17.5	29.3	**p=0.006**[*]	-	**HR=1.30, p=0.046**[*]	-	**HR=1.31, p=0.02**[*]	-
Boström et al. (2012)	1986-2008	546	66	T0-T1 39.4; T2 21.2; T3 28.2; T4 11.2	NR	Neoadj NR; Adj NR	50	-	-	HR=1.1, p=0.41[†]	-	HR=1.3, p=0.10[†]	-
Lee et al. (2012)	1989-2008	602	62.2	T0-T2 56.8; T3/T4 43.2	G1/G2 15.6; G3 84.4	Neoadj 0.0; Adj NR	56.0	HR=0.93, p=0.65;[‡] HR=0.91, p=0.61[§]	HR=0.86, p=0.47[‖]	HR=1.21, p=0.27;[‡] HR=0.94, p=0.73[§]	HR=0.95, p=0.83[‖]	HR=1.01; p=0.93[†]	-
Baumann et al. (2013)	1990-2008	442	67.0	T0 7.9; Ta 2.3; Tis 15.4; T1 8.1; T2 18.8; T3 31.7; T4 15.8	NR	Neoadj 8.8; Adj 24.0	26.4	HR=0.89, p=0.65[*]	-	-	-	-	-
Rink et al. (2013)	2000-2008	1506	66.4	T0 5.2; Ta 4.1; Tis 11.2; T1 11.3; T2 26.6; T3 30.5; T4 11.2	None 5.2; LG 1.9; HG 92.9	Neoadj 0.0; Adj 21.4	34.3	HR=1.26 (0.96-1.66);[¶] **HR=1.47 (1.12-1.94)**[**]	**HR=1.54 (1.08-2.19)**;[††] **HR=1.70 (1.23-2.36)**;[‡‡] **HR=2.22 (1.62-3.02)**[§§]	HR=1.22 (0.91-1.63);[¶] **HR=1.41 (1.04-1.90)**[**]	**HR=1.55 (1.04-2.32)**;[††] **HR=1.53 (1.04-2.24)**;[‡‡] **HR=2.07 (1.44-2.99)**[§§]	HR=1.13 (0.89-1.44);[¶] HR=1.25 (0.97-1.60)[**]	HR=1.23 (0.90-1.69);[††] **HR=1.36 (1.01-1.83)**;[‡‡] **HR=1.51 (1.13-2.01)**[§§]
Kim et al. (2014)	1990-2011	139	65	T0 17.3; Tis 15.8; T1 7.9; T2 12.2; T3 41.0; T4 5.8	NR	Neoadj 100; Adj 0.0	46	p=0.6[‖‖]	p=0.11;[¶¶] p=0.2[***]	p=0.9[‖‖]	p=0.4;[¶¶] p=0.4[***]		

G1=grade 1; G2=grade 2; G3=grade 3; G4=grade 4; neoadj=neoadjuvant chemotherapy; NR=not reported; adj=adjuvant chemotherapy; HR=hazard ratio; LG=low grade; HG=high grade.
Bold: statistically significant relationship.
[*] Smokers vs. non-smokers.
[†] Non-smokers vs. smokers.
[‡] Never vs. former smokers.
[§] Never vs. current smokers.
[‖] Never smokers vs. ≥40 pack-years; also significant for never smokers vs. <10, <20, <30, and <40 pack-years.
[¶] Former vs. never smokers.
[**] Current vs. never smokers.
[††] Heavy short-term (>20 cigarettes per day for ≤20 years) vs. light short-term (≤20 cigarettes per day for ≤20 years) smokers.
[‡‡] Light long-term (≤20 cigarettes per day for >20 years) vs. light short-term smokers.
[§§] Heavy long-term (>20 cigarettes per day for >20 years) vs. light short-term smokers.
[‖‖] Current vs. former vs. never smokers.
[¶¶] Number of packs per day.
[***] Number of pack-years.

Table 4 – Selected studies reporting associations of smoking cessation and outcomes of patients with urothelial carcinoma of the bladder treated with transurethral resection of the bladder or radical cystectomy

Selected studies and their smoking cessation categories				Outcomes			
Intervention	Study*	Cessation group†	Comparator group†	Disease Recurrence	Disease Progression	Cancer-specific mortality	Overall mortality
Transurethral resection of the bladder	Fleshner et al. (1999)	1-10 yr before	1 yr before to 3 mo after	HR=1.01, p=0.89	-	-	-
		1-10 yr before	Current smokers	**HR=0.71, p=0.03**	-	-	-
	Chen et al. (2007)	>1 yr before	1 yr before to 3 mo after	HR=1.4, p=0.35	-	-	-
		1 yr before to 3 mo after	Current smokers	**HR=0.5, p=0.01**	-	-	-
	Lammers et al. (2011)	≥15 yr before	<15 yr before	p=0.34	-	-	-
	Rink et al. (2012)	≥10 yr before	Current smokers	**HR=0.40, p<0.001**	HR=0.51, p=0.11	-	-
		<10 yr before		HR=1.44, p=0.05	HR=1.26, p=0.48	-	-
	Rink et al. (2013)	≥10 yr before	Current smokers	**HR=0.66 (0.52-0.84)**	**HR=0.42 (0.22-0.83)**	-	HR=0.98 (0.72-1.34)
		<10 yr before		HR=1.30 (1.09-1.53)	HR=0.99 (0.65-1.50)	-	HR=1.02 (0.79-1.30)
	Grotenhuis et al. (2014)	≥10 yr before	Current smokers	HR=1.22 (0.88-1.68)	HR=1.40 (0.85-2.30)	-	-
		<10 yr before		HR=1.38 (0.97-1.95)	HR=1.68 (0.92-3.07)	-	-
Radical cystectomy	Rink et al. (2013)	≥10 yr before	Current smokers	**HR=0.44 (0.31-0.62)**	-	**HR=0.42 (0.29-0.63)**	**HR=0.69 (0.52-0.91)**
		<10 yr before		HR=1.08 (0.88-1.33)	-	HR=1.09 (0.86-1.37)	HR=1.05 (0.85-1.28)

HR=hazard ratio.
Bold: statistically significant relationship.
* Refer to Tables 2 and 3 for study and patient characteristics.
† Smoking cessation time periods are relative to the time of diagnosis.

the effects of smoking on UCB prognosis in conjunction with other demographic characteristics, such as race and ethnicity, other clinical risk factors, such as obesity [46], and multimodal therapies including neoadjuvant and adjuvant systemic chemotherapy require further investigation. Despite advances in surgical techniques and improvements in systemic chemotherapies, up to 50% of patients with MIBC experience disease recurrence within 5 yr after surgery, and the majority of these patients eventually die of UCB [69]. Similar to NMIBC, different decision-making tools have been developed to assist clinicians in patient counseling and estimation of multimodal treatment success in MIBC [70–72], but are limited by imperfect discrimination. Combination with blood, tissue, and/or urine biomarkers improves these tools regarding outcome prognostication and patient selection for multimodal therapies [73]. A recently published study on MIBC patients treated with RC found that the combination of smoking information and tissue marker status achieved the highest level of discrimination and significantly improved outcome prediction [74].

4. Conclusions

Cigarette smoking is the best-established, individually modifiable risk factor for UCB development, although potential relationships with other inherent and environmental factors remain ambiguous. In addition, there is a growing body of evidence that smoking negatively affects UCB outcomes. According to the currently available literature, smoking status and cumulative lifetime smoking exposure at diagnosis and at different times during treatment seem to affect disease recurrence, progression, and survival. However, the evidence is quite heterogeneous, mainly because of the exclusively retrospective study designs. While studies have demonstrated that long-term smoking cessation reduces the risk of UCB carcinogenesis and improves prognosis, prospective evaluation of this relationship is lacking. Future research regarding the effects of smoking needs to continue to improve our understanding, and prospective studies need to address currently unanswered questions.

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Study concept and design: Rink, Crivelli.
Acquisition of data: Crivelli, Rink.
Analysis and interpretation of data: Rink, Crivelli.
Drafting of the manuscript: Rink, Crivelli.
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