CrossMark

ORIGINAL PAPER

Smoking status, usual adult occupation, and risk of recurrent urothelial bladder carcinoma: data from The Cancer Genome Atlas (TCGA) Project

Amber N. Wilcox[1] · Debra T. Silverman[1] · Melissa C. Friesen[1] · Sarah J. Locke[1] ·
Daniel E. Russ[2] · Noorie Hyun[1] · Joanne S. Colt[1] · Jonine D. Figueroa[3] ·
Nathaniel Rothman[1] · Lee E. Moore[1] · Stella Koutros[1]

Abstract

Purpose Tobacco smoking and occupational exposures are the leading risk factors for developing urothelial bladder carcinoma (UBC), yet little is known about the contribution of these two factors to risk of UBC recurrence. We evaluated whether smoking status and usual adult occupation are associated with time to UBC recurrence for 406 patients with muscle-invasive bladder cancer submitted to The Cancer Genome Atlas (TCGA) project.

Methods Kaplan–Meier and Cox proportional hazard methods were used to assess the association between smoking status, employment in a high-risk occupation for bladder cancer, occupational diesel exhaust exposure, and 2010 Standard Occupational Classification group and time to UBC recurrence.

Results Data on time to recurrence were available for 358 patients over a median follow-up time of 15 months. Of these, 133 (37.2%) experienced a recurrence. Current smokers who smoked for more than 40 pack-years had an increased risk of recurrence compared to never smokers (HR 2.1, 95% CI 1.1, 4.1). Additionally, employment in a high-risk occupation was associated with a shorter time to recurrence (log-rank $p = 0.005$). We found an increased risk of recurrence for those employed in occupations with probable diesel exhaust exposure (HR 1.8, 95% CI 1.1, 3.0) and for those employed in production occupations (HR 2.0, 95% CI 1.1, 3.6).

Conclusions These findings suggest smoking status impacts risk of UBC recurrence, although several previous studies provided equivocal evidence regarding this association. In addition to the known causal relationship between occupational exposure and bladder cancer risk, our study suggests that occupation may also be related to increased risk of recurrence.

Keywords Bladder cancer · Recurrence · Occupation · Smoking status · Diesel exhaust

✉ Stella Koutros
koutross@mail.nih.gov

1   Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Rockville, MD, USA

2   Division of Computational Bioscience, Department of Health and Human Services, Center for Information Technology, National Institutes of Health, Bethesda, MD, USA

3   Usher Institute of Population Health Sciences and Informatics, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

Introduction

Tobacco smoking and occupational exposures are the leading risk factors for urothelial bladder carcinoma (UBC) incidence. Smoking accounts for about 50% of bladder cancer cases in both men and women in the USA [1]. Following smoking, occupational exposures are the second most important risk factor for UBC, with up to 25% of all cases being attributed to these exposures [2]. Occupational groups that have been linked to increased incidence of UBC include dyestuffs workers, aromatic amine manufacturing workers, painters, aluminum workers, and drivers of trucks, and other motor vehicles [3].

Little is known about the contribution of smoking and occupational exposures to the risk of UBC recurrence. A

🍾 Springer

recent meta-analysis of the evidence for smoking found that both smoking status and pack-years appear to have an effect on disease prognosis (in terms of recurrence and progression) in patients with non-muscle-invasive bladder carcinoma (NMIBC) [4]. In contrast, the studies that include patients with muscle-invasive bladder carcinoma (MIBC) had equivocal results about the association of smoking with disease recurrence [4]. We are not aware of any studies that have evaluated the impact of occupation or specific occupational exposures on risk of recurrence.

UBC is highly recurrent and costly to treat, making research into possible risk factors for recurrence an important public health priority. The objective of our study is to evaluate whether smoking status and usual adult occupation are associated with time to UBC recurrence for patients with muscle-invasive bladder cancer in The Cancer Genome Atlas (TCGA) project.

Materials and methods

Study population

There were 406 MIBC cases, diagnosed between 2010 and 2014, included in TCGA (https://tcga-data.nci.nih.gov/, accessed 06/05/2015). Patients included in TCGA were those who underwent surgical resection with either transurethral resection of the bladder (TURB) or radical cystectomy (RC). No patients received prior chemotherapy or radiotherapy treatment for their disease, although prior intravesical Bacille Calmette–Guerin (BCG) was allowed. Of 406 unique records, 358 cases had data on recurrence and time to recurrence. Recurrence was defined as first new tumor event: locoregional recurrence or distant metastasis. Subjects were censored at date of first recurrence after follow-up. Those who did not experience recurrence were censored at last known follow-up date or date of death. A total of 133 patients had a recurrence, while 225 patients did not have a recurrence.

Exposure assessment

Smoking status was assessed by patients' self-reported smoking history as either: "lifelong non-smoker (<100 cigarettes smoked in lifetime)," "current smoker (includes daily and non-daily smokers)", "current reformed smoker for >15 years," "current reformed smoker for ≤15 years," "current reformed smoker (duration not specified)," or "smoking history not documented." For current and former smokers, additional questions were asked to determine age of onset of tobacco smoking and year of quitting tobacco smoking. This information was combined with the number of cigarettes smoked per day to calculate pack-years

smoked, which represents lifetime tobacco exposure. Patients reported occupational information such as job title of usual occupation ("occupation in which the patient was employed for the majority of their working years"), industry of usual occupation, and chemical exposures ("any chemical exposure the patient had during their working years in their primary occupation"). Publicly available software (http://soccer.nci.nih.gov) was used to code this free-text job information to two-digit level groups within the 2010 Standard Occupational Classification (SOC) system (http://www.bls.gov/soc) [5]. Some job descriptions assigned SOC codes with lower certainty ($n = 79$) received expert review (S.J.L) to determine the most appropriate group assignment. Subjects were further dichotomized into high-risk occupation group (no/yes) based on employment in an occupation with a priori bladder cancer risk in the literature (Online Resource 1). Approximately 19% (69/358) of subjects with data on recurrence were employed in a high-risk occupation. An additional variable was created to indicate exposure to diesel exhaust, as it was the most prevalent high-risk occupational exposure in the data set and a known carcinogen. This was dichotomized (no/yes) based on expert knowledge of jobs with either moderate or high probability of occupational diesel exposure [6]. Approximately 14% (51/358) of subjects with data on recurrence were probably exposed to diesel exhaust. Among these subjects, 33 were also employed in an a priori high-risk occupation and 18 were employed in other jobs.

Statistical analysis

We plotted the Schoenfeld residuals to detect violations of proportional hazard assumptions for the exposures and potential covariates, and no major violations were observed. We calculated both unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazard models, with separate models for each independent exposure variable of interest: smoking, employment in a high-risk occupation, diesel exhaust exposure, and each individual major two-digit SOC grouping. A competing risks model was also considered, which produced similar results when compared to the Cox proportional hazards model (data not shown). The following characteristics were considered as potential confounders in the adjusted models: smoking status (never, former smoker <30 pack-years, former smoker ≥30 pack-years, current smoker <40 pack-years, current smoker ≥40 pack-years), age at diagnosis (<55, 56–65, 66–75,>75), race (White, Black, Asian), body mass index (14–24, 25–29, ≥30), gender, country of residence (USA or other), history of other malignancy, history of non-muscle-invasive bladder cancer, histologic subtype (papillary, non-

Table 1 Characteristics of bladder cancer recurrences

Characteristic	No recurrence N = 226	Recurrence N = 133	P value
Age at diagnosis			
<55	36 (15.9)	10 (7.5)	
56–65	53 (23.5)	47 (35.3)	
66–75	71 (31.4)	48 (36.1)	
>75	66 (29.2)	28 (21.1)	0.05
Country			
USA	159 (70.4)	100 (75.2)	
Other	67 (29.7)	33 (24.8)	0.52
Race			
White	176 (77.9)	107 (80.5)	
Black	10 (4.4)	10 (7.5)	
Asian	34 (15.0)	9 (6.8)	
Missing	6 (2.7)	7 (5.3)	0.51
Gender			
Male	172 (76.1)	97 (72.9)	
Female	54 (23.9)	36 (27.1)	0.65
Smoking			
Never	63 (27.9)	33 (24.8)	
Former (< 30 pack-years)	40 (17.7)	22 (16.5)	
Former (≥ 30 pack-years)	34 (15.0)	40 (30.1)	
Current (< 40 pack-years)	22 (9.7)	9 (6.8)	
Current (≥ 40 pack-years)	15 (6.6)	14 (10.5)	
Missing	52 (23.0)	15 (11.3)	0.02
Pathologic stage (AJCC)			
Stage II	93 (41.2)	31 (23.3)	
Stage III	79 (35.0)	39 (29.3)	
Stage IV	54 (23.9)	63 (47.4)	<.0001
Histologic subtype			
Non-papillary	141 (62.4)	101 (75.9)	
Papillary	85 (37.6)	32 (24.1)	0.07
History of NMI			
No	156 (69.0)	74 (55.6)	
Yes	34 (15.0)	28 (21.1)	
Missing	36 (15.9)	31 (23.3)	0.52
History of other malignancy			
No	174 (77.0)	89 (66.9)	
Yes	52 (23.0)	44 (33.1)	0.35
High-risk occupation			
No	104 (46.0)	55 (41.4)	
Yes	33 (14.6)	36 (27.1)	
Missing	89 (39.4)	42 (31.6)	0.01

AJCC American Joint Committee on Cancer, *NMI* Non-muscle invasive

p values calculated using log-rank tests

papillary), stage of disease based on the AJCC cancer staging system (II, III, IV), and treatment (immunotherapy, chemotherapy, radiation, combination, unknown). The pack-year cut points for the categorical analysis were selected based on the median pack-year exposure within each stratum. The model of diesel exhaust exposure was also adjusted for employment in high-risk occupations other than those involving diesel exhaust exposure. Models for each independent exposure variable retained covariates that impacted the parameter estimates by more than 10%.
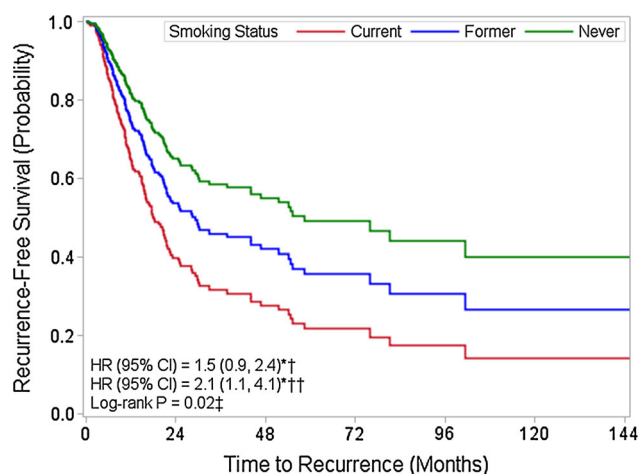
Fig. 1 Adjusted Kaplan–Meier plot for time to first recurrence by smoking status. * Adjusted for age at diagnosis (<55, 56–65, 66–75, >75), stage of disease (II, III, IV), and treatment (immunotherapy, chemotherapy, radiation, combination, unknown). † Former smokers with ≥30 pack-years compared to never smokers. †† Current smokers with ≥40 pack-years compared to never smokers. ‡ Comparing all smoking levels (never, former with <30 pack-years, former with ≥30 pack-years, current with <40 pack-years, current with ≥40 pack-years)

For models evaluating smoking, employment in a high-risk occupation, and diesel exposure, we also conducted stratified analyses by the above listed variables. Likelihood ratio tests were used to assess differences between strata (P-interaction). All tests were two-sided and conducted at the α = 0.05 level.

Results

In this study, 133 out of 358 (37.2%) patients experienced a recurrence. The median follow-up time was 15 months (IQR 8–27), and the median time to recurrence was 11 months (IQR 7–20). The characteristics of patients by recurrence status are presented in Table 1. Patients who experienced a recurrence presented with primary tumors that were of a higher stage than patients who did not experience a recurrence (47 vs. 24% in stage IV, respectively). In addition, patients who experienced a recurrence more commonly presented with the non-papillary bladder cancer subtype compared to patients who did not experience a recurrence (76 vs. 62%, respectively). No differences were detected when comparing the distribution of these characteristics to patients with missing data (n = 47) on recurrence (data not shown).

Figure 1 shows the association of smoking status with time to recurrence. Current smokers with over 40 pack-years of exposure had a twofold increased risk of recurrence when compared to never smokers (HR 2.1, 95% CI 1.1, 4.1). Former smokers with over 30 pack-years of

exposure also had an increased risk of recurrence when compared to never smokers, although this finding was not statistically significant (HR 1.5, 95% CI 0.9, 2.4).

Table 2 shows the association between high-risk occupation, diesel exhaust exposure, and major SOC group with time to recurrence. Employment in a high-risk occupation was associated with a shorter time to recurrence (log-rank p = 0.005, Fig. 2). In addition, probable diesel exposure was associated with an 80% increased risk of recurrence (HR 1.8, 95% CI 1.1, 2.8). Among the major SOC groups, employment in production occupations was associated with an increased risk of recurrence (HR 2.0, 95% CI 1.1, 3.6). In univariate analysis, employment in construction and extraction occupations was associated with a twofold increased risk of recurrence (HR 2.1, 95% CI 1.2, 3.6); however, this became only borderline nonsignificant after adjusting for age, stage, and treatment.

No additional noteworthy findings were observed in stratified models, and no significant interactions were observed.

Discussion

Smoking status and usual adult occupation were both found to be associated with time to UBC recurrence for patients with MIBC. Current smoking of over 40 pack-years was associated with an increased risk of recurrence. In addition, employment in a high-risk occupation, occupations with probable diesel exhaust exposure, and production occupations were each found to be associated with an increased risk of recurrence.

There is some evidence in the literature of the effect of smoking on UBC recurrence, although most studies focus on the impact of smoking on recurrence in NMI disease, given the high rate of recurrence in this subgroup. Five studies have included MIBC patients when examining this association [7–11]. Two of them found no effect of smoking status on risk of recurrence [10, 11], while one did observe a difference [9]; these studies, however, had limited information on smoking (ever/never). Of the two studies with more detailed data on smoking history, one found no association among current smokers compared to non-smokers (HR 0.91, 95% CI 0.63, 1.31) [7], while the other study found an increased risk of recurrence for heavy long-term smokers compared to light short-term smokers (HR 2.22, 95% CI 1.62, 3.02) [8]. Our findings are consistent with the latter study in that we found an increased risk of recurrence among current smokers of over 40 pack-years when compared to never smokers (HR 2.1, 95% CI 1.1, 4.1). The exact mechanism underlying the effect of smoking on UBC recurrence is not known, although it is theorized that exposure to carcinogens in cigarettes, such as

Table 2 Hazard ratios for time to recurrence by high-risk occupation, diesel exposure, and major SOC group

Exposure	No recurrence/recurrence	Unadjusted HR 95% CI	Adjusted HR[a] 95% CI
High-risk occupation[b]			
No	104/55	Ref	Ref
Yes	33/36	1.9 (1.2, 2.9)	2.0 (1.3, 3.2)
Diesel exhaust exposure[c,d]			
No/Low probability	109/68	Ref	Ref
Moderate/High probability	28/23	1.5 (0.9, 2.3)	1.8 (1.1, 3.0)
Major SOC group			
11-Management occupations[e,f]	8/6	0.9 (0.4, 2.1)	0.6 (0.2, 1.6)
13-Business and financial operations occupations	6/6	1.2 (0.6, 2.8)	1.1 (0.5, 2.6)
17-Architecture and engineering occupations	6/4	0.9 (0.4, 2.5)	0.9 (0.3, 2.5)
23-Legal occupations[e,f]	3/2	1.3 (0.3, 5.1)	0.8 (0.2, 3.5)
25-Education, training, and library occupations	6/3	1.0 (0.3, 3.1)	1.0 (0.3, 3.2)
29-Healthcare practitioners and technical occupations[e,f,g]	5/4	1.1 (0.4, 2.9)	1.1 (0.4, 3.3)
35-Food preparation and serving related occupations[c,f]	4/2	0.8 (0.2, 3.3)	0.7 (0.2, 2.8)
37-Building and grounds cleaning and maintenance occupations[e]	2/1	1.0 (0.1, 7.0)	1.3 (0.2, 9.6)
41-Sales and related occupations	14/6	0.7 (0.3, 1.6)	0.8 (0.3, 1.8)
43-Office and administrative support occupations	12/4	0.5 (0.2, 1.2)	0.6 (0.2, 1.5)
45-Farming, fishing, and forestry occupations	12/3	0.6 (0.2, 1.9)	0.7 (0.2, 2.4)
47-Construction and extraction occupations	8/14	2.1 (1.2, 3.6)	1.7 (0.97, 3.1)
49-Installation, maintenance, and repair occupations	8/2	0.4 (0.1, 1.7)	0.7 (0.2, 2.7)
51-Production occupations	12/12	1.5 (0.8, 2.7)	2.0 (1.1, 3.6)
53-Transportation and material moving occupations[c,f]	6/9	1.7 (0.8, 3.3)	1.2 (0.6, 2.4)
55-Military-specific occupations	4/2	1.1 (0.3, 4.4)	1.2 (0.3, 4.8)
99-Housewives[f]	6/6	1.4 (0.6, 3.1)	1.1 (0.4, 2.5)

[a] Adjusted for age at diagnosis (<55, 56–65, 66–75, >75), stage of disease (II, III, IV), and treatment (immunotherapy, chemotherapy, radiation, combination, unknown)

[b] Additionally adjusted for gender

[c] Additionally adjusted for body mass index

[d] Additionally adjusted for employment in high-risk occupations other than those involving diesel exhaust exposure

[e] Additionally adjusted for smoking

[f] Additionally adjusted for history of non-muscle-invasive bladder cancer

[g] Additionally adjusted for history of other malignancy

aromatic amines, may have cancer-promoting effects [12]. The potential influence of the timing of smoking cessation on risk of UBC recurrence is also not known.

There is strong evidence of an increased risk of bladder cancer incidence among certain occupations, such as dyestuffs workers, aromatic amine manufacturing workers, rubber workers, leather workers, painters, truck drivers, and aluminum workers [3]. There has also been some evidence of an increased risk among metal workers, printers, chemical workers, construction workers, miners, and textile workers, among others [3]. Our study found an increased risk of recurrence among people who held some of these high-risk jobs as their usual adult occupation. In addition, we found a similar increased risk of recurrence for those employed in production occupations, which include job titles such as: textile industry worker, chemical machine operator, and machinist. There is a causal relationship between occupation and bladder cancer risk; our study suggests that occupation may also be related to adverse outcomes after diagnosis. Some of these high-risk occupations have exposures that are known to be related to UBC incidence [13, 14], others have exposures that are likely highly heterogeneous. More work is needed to identify the specific exposures that drive these associations and how these exposures may promote UBC.

There is growing evidence in the literature of an association between occupational exposure to diesel exhaust and risk of bladder cancer. A meta-analysis examining this
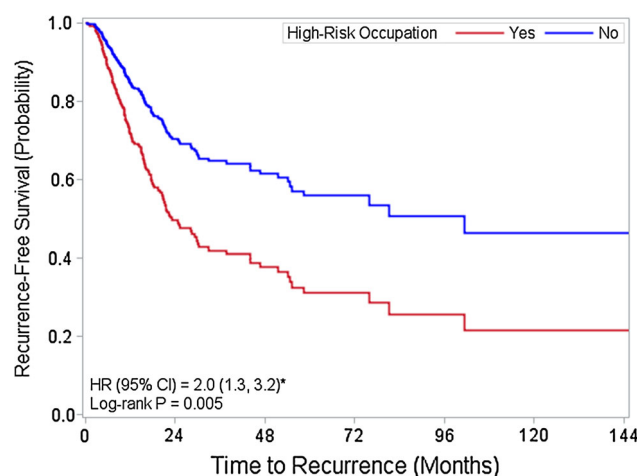
Fig. 2 Adjusted Kaplan–Meier plot for time to recurrence by high-risk occupation. * Adjusted for age at diagnosis (<55, 56–65, 66–75, >75), gender, stage of disease (II, III, IV), and treatment (immunotherapy, chemotherapy, radiation, combination, unknown)

association found effect estimates to suggest an overall relative risk of approximately 1.1–1.3 [15]. Additionally, the summary relative risk for high diesel exposure was 1.44 (95% CI 1.18, 1.76) [15]. Our findings indicate an increased risk of recurrence among those employed in an occupation with probable diesel exhaust exposure. No association was found, however, for employment in transportation and material moving occupations, which may have exposure to diesel. This disparity is likely due to the fact that diesel exhaust exposure spans many different job titles with heterogeneous exposures. Although the mechanism by which diesel exhaust exposure might influence recurrence is unknown, a p53-dependent mechanism has been suggested [16, 17] and is a common feature of MI disease [18].

This study is the first to our knowledge to evaluate the association between usual occupation and UBC recurrence. Although we were able to categorize occupation according to standardized groupings, information on tasks performed within a broad occupational grouping was lacking and limited the ability to characterize specific exposures associated with high-risk occupations. There was also minimal data available on duration of employment and on industry for many subjects; however, the use of the usual adult occupation is likely to be most representative of the subjects' job history and exposure circumstance. In addition, the data on exposure to diesel exhaust does not reflect the changes over time in diesel engines and in emissions. A strength of this study was the availability of information on both smoking status and cumulative exposure in terms of pack-years. The smoking data were limited, however, by the fact that changes in smoking status over time or smoking cessation were not collected. Other limitations of

this study are the relatively small sample size, limited power, and missing data on the exposures of interest. The lack of a representative sample may also limit the ability to compare the results of this study to that of other population-based studies. Despite this limitation, we observed an association between high-risk occupation and recurrence that is comparable in magnitude to studies of bladder cancer incidence [19], which lends credence to our findings. In addition, the effect observed here with smoking is similar to the largest of only two studies which have evaluated more detailed smoking information and risk of recurrence [8]. Lastly, data collected in TCGA only indicate the occurrence of death. Disease-specific survival was unavailable, and thus, we were unable to assess whether smoking and occupation are associated with bladder cancer survival, in addition to recurrence.

It will be important for future studies to evaluate the association between smoking and occupational exposures with UBC recurrence in patients with NMIBC because of the high cost of long-term medical surveillance of large numbers of survivors resulting from high recurrence rate in this subgroup. Work is also needed to determine whether these important bladder cancer risk factors are associated with certain molecular tumor characteristics that influence progression of disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval TCGA is a public resource and all approvals were acquired by the original study.

Informed consent Informed consent was obtained from all individual participants included in each participating TCGA study.

References

1. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC (2011) Association between smoking and risk of bladder cancer among men and women. JAMA 306(7):737–745. doi:10.1001/jama.2011.1142

2. Silverman DT, Levin LI, Hoover RN, Hartge P (1989) Occupational risks of bladder cancer in the United States: I. White men. J Natl Cancer Inst 81(19):1472–1480

3. Silverman DT, Devesa SS, Moore LE, Rothman N (2006) Bladder cancer. In: Schottenfeld D, Fraumeni JFJ (eds) Cancer epidemiology and prevention, 3rd edn. Oxford University Press, New York, pp 1101–1127

4. Crivelli JJ, Xylinas E, Kluth LA, Rieken M, Rink M, Shariat SF (2014) Effect of smoking on outcomes of urothelial carcinoma: a

systematic review of the literature. Eur Urol 65(4):742–754. doi:10.1016/j.eururo.2013.06.010

5. Russ DE, Ho KY, Colt JS, Armenti KR, Baris D, Chow WH, Davis F, Johnson A, Purdue MP, Karagas MR, Schwartz K, Schwenn M, Silverman DT, Johnson CA, Friesen MC (2016) Computer-based coding of free-text job descriptions to efficiently identify occupations in epidemiological studies. Occup Environ Med 73(6):417–424. doi:10.1136/oemed-2015-103152

6. Pronk A, Coble J, Stewart PA (2009) Occupational exposure to diesel engine exhaust: a literature review. J Expo Sci Environ Epidemiol 19(5):443–457. doi:10.1038/jes.2009.21

7. Lee C, Kim KH, You D, Jeong IG, Hong B, Hong JH, Ahn H, Kim CS (2012) Smoking and survival after radical cystectomy for bladder cancer. Urology 80(6):1307–1312. doi:10.1016/j.urology.2012.08.026

8. Rink M, Zabor EC, Furberg H, Xylinas E, Ehdaie B, Novara G, Babjuk M, Pycha A, Lotan Y, Trinh QD, Chun FK, Lee RK, Karakiewicz PI, Fisch M, Robinson BD, Scherr DS, Shariat SF (2013) Impact of smoking and smoking cessation on outcomes in bladder cancer patients treated with radical cystectomy. Eur Urol 64(3):456–464. doi:10.1016/j.eururo.2012.11.039

9. Yafi FA, Aprikian AG, Chin JL, Fradet Y, Izawa J, Estey E, Fairey A, Rendon R, Cagiannos I, Lacombe L, Lattouf JB, Bell D, Drachenberg D, Kassouf W (2011) Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicentre experience. BJU Int 108(4):539–545. doi:10.1111/j.1464-410X.2010.09912.x

10. Baumann BC, Guzzo TJ, He J, Keefe SM, Tucker K, Bekelman JE, Hwang WT, Vaughn DJ, Malkowicz SB, Christodouleas JP (2013) A novel risk stratification to predict local-regional failures in urothelial carcinoma of the bladder after radical cystectomy. Int J Radiat Oncol Biol Phys 85(1):81–88. doi:10.1016/j.ijrobp.2012.03.007

11. Boorjian SA, Kim SP, Weight CJ, Cheville JC, Thapa P, Frank I (2011) Risk factors and outcomes of urethral recurrence following radical cystectomy. Eur Urol 60(6):1266–1272. doi:10.1016/j.eururo.2011.08.030

12. Escudero DO, Shirodkar SP, Lokeshwar VB (2011) Bladder carcinogenesis and Molecular pathways. In: Lokeshwar VB, Merseburger AS, Haurmann SH (eds) Bladder tumors: molecular aspects and clinical management. Humana Press, New York, pp 23–41

13. Colt JS, Friesen MC, Stewart PA, Donguk P, Johnson A, Schwenn M, Karagas MR, Armenti K, Waddell R, Verrill C, Ward MH, Freeman LE, Moore LE, Koutros S, Baris D, Silverman DT (2014) A case-control study of occupational exposure to metal-working fluids and bladder cancer risk among men. Occup Environ Med 71(10):667–674. doi:10.1136/oemed-2013-102056

14. Naito S, Tanaka K, Koga H, Kotoh S, Hirohata T, Kumazawa J (1995) Cancer occurrence among dyestuff workers exposed to aromatic amines. A long term follow-up study. Cancer 76(8):1445–1452

15. Boffetta P, Silverman DT (2001) A meta-analysis of bladder cancer and diesel exhaust exposure. Epidemiology 12(1):125–130

16. Schroeder JC, Conway K, Li Y, Mistry K, Bell DA, Taylor JA (2003) p53 mutations in bladder cancer: evidence for exogenous versus endogenous risk factors. Cancer Res 63(21):7530–7538

17. Yun YP, Lee JY, Ahn EK, Lee KH, Yoon HK, Lim Y (2009) Diesel exhaust particles induce apoptosis via p53 and Mdm2 in J774A.1 macrophage cell line. Toxicol Vitro Inter J Pub Assoc BIBRA 23(1):21–28. doi:10.1016/j.tiv.2008.09.018

18. Knowles MA, Hurst CD (2015) Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nat Rev Cancer 15(1):25–41. doi:10.1038/nrc3817

19. Figueroa JD, Koutros S, Colt JS, Kogevinas M, Garcia-Closas M, Real FX, Friesen MC, Baris D, Stewart P, Schwenn M, Johnson A, Karagas MR, Armenti KR, Moore LE, Schned A, Lenz P, Prokunina-Olsson L, Banday AR, Paquin A, Ylaya K, Chung JY, Hewitt SM, Nickerson ML, Tardon A, Serra C, Carrato A, Garcia-Closas R, Lloreta J, Malats N, Fraumeni JF Jr, Chanock SJ, Chatterjee N, Rothman N, Silverman DT (2015) Modification of occupational exposures on bladder cancer risk by common genetic polymorphisms. J Natl Cancer Inst. doi:10.1093/jnci/djv223