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1 **Tar, nicotine and carbon monoxide yield of UK cigarettes and the**
2 **risk of non-muscle-invasive and muscle-invasive bladder cancer.**

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33 Sciences, University of Birmingham.

34 **Abstract**

35 **Objective**

36 Cigarette smoking is a major risk factor for bladder cancer (BC), however the impact of
37 cigarette content remains unclear. This study aims to investigate tar, nicotine and carbon
38 monoxide (TNCO) yields of different filtered cigarettes in relation to BC risk.

39 **Methods**

40 From the Bladder Cancer Prognosis Programme 575 non-muscle-invasive BC (NMIBC)
41 cases, 139 muscle-invasive BC (MIBC) cases and 130 BC-free controls with retrospective
42 data on smoking behaviour and cigarette brand were identified. Independently measured
43 TNCO yields of cigarettes sold in the UK were obtained through the UK Department of
44 Health and merged with the BCPP dataset to estimate daily intake of TNCO.

45 **Results**

46 BC risk increased by TNCO intake category for NMIBC cases (p for trend <0.050 in all
47 multivariate models) but only for daily intake of tar for MIBC cases (p=0.046) in multivariate
48 models. No difference in risk is observed between smokers of low tar/low nicotine and high
49 tar/high nicotine cigarettes compared to never smokers, neither for NMIBC (p=0.544) nor
50 MIBC (p=0.449).

51 **Conclusion**

52 High daily intake of TNCO additionally increases both NMIBC and MIBC risk compared to
53 low daily intake. However since there is no difference in BC risk between low tar/low
54 nicotine and high tar/high nicotine cigarette smokers it remains unclear whether smoking
55 behaviour or TNCO yield of cigarettes explains this association.

56

57 **Keywords:** urinary bladder neoplasms; smoking; epidemiology; toxicology

58 **Background**

59 Bladder cancer (BC) ranks fifth in the list of most common cancers in Western countries and
60 active smoking is indicated as its most common risk factor together with occupational
61 exposure to carcinogenic chemicals and some diet-related factors (Al-Zalabani et al. 2016;
62 Antoni et al. 2017). The impact of cigarette smoking has been quantified in a large number of
63 studies, and a recent meta-analysis showed that current smokers have a three-fold increased
64 risk of developing BC compared to never smokers (van Osch et al. 2016).

65

66 The relation between the amount of smoking and cancer risk has been investigated
67 extensively, and is mostly characterised by smoking duration in years, smoking intensity in
68 cigarettes per day, or pack years (an amalgamation of duration and intensity). However, the
69 type of cigarette or cigarette composition is taken into account less often. Therefore, the
70 evidence on the impact of different types of cigarettes, with regard to the composition of the
71 cigarette smoke, on BC risk remains weak. Previous studies have shown lower BC risks for
72 filter versus non-filter cigarette smokers and also when comparing blond tobacco to black
73 tobacco (Clavel et al. 1989; García-Closas et al. 2005; Howe et al. 1980; Vineis et al. 1984).
74 Two observational studies quantified BC risk for different intakes of tar and nicotine, of
75 which one showed a linearly increasing trend in risk related to the amount of tar and nicotine
76 and the other study showed no association between BC risk and cumulative tar intake
77 (Castelao et al. 2001; Zeegers et al. 2002). By introducing the filter tip, which changed
78 cigarette design but not necessarily the contents, smoking-related mortality has moderately
79 decreased (Tang et al. 1995), although there are studies indicating that the levels of
80 carcinogens in contemporary cigarettes might have become higher (Baris et al. 2009).
81 Nevertheless, it remains unclear whether differences in cigarette content are related to
82 meaningful differences in BC risk at population level. Therefore, we calculated the levels of

- 83 tar, nicotine and carbon monoxide (TNCO) in mainstream smoke in a UK-based cohort study
- 84 and aimed to investigate whether these levels influence BC risk.

85 **Methods**

86 **Study population**

87 This case-control study was conducted within the framework of the West Midlands Bladder
88 Cancer Prognosis Programme (BCPP), an ongoing BC patient cohort study conducted in
89 multiple centres in the West Midlands, United Kingdom. Further details of the BCPP are
90 described elsewhere (Zeegers et al. 2010). In summary, the study population contained 1,544
91 adult individuals who were referred to one of the participating urology centres because of
92 symptoms indicative of BC (predominantly haematuria). Of these 1,544 individuals, there
93 were 1008 patients diagnosed with non-muscle-invasive bladder cancers (NMIBC), 275
94 muscle-invasive bladder cancer (MIBC) patients and 205 individuals were subsequently
95 diagnosed as free from any form of cancer after histological tests at the urology clinic and
96 selected as controls. Additionally, 57 patients were diagnosed with other primary cancers
97 (e.g. prostate cancer) or had missing data on important staging data so could not be confirmed
98 to have BC(Figure 1).

99 Cases and controls whom did not provide data on cigarette brand and smoking status
100 were excluded for analysis. Of the 205 potential controls, 130 had a clear specification of
101 control status and provided data on smoking status and cigarette brand. Of these 130 controls,
102 34 had benign papillomas, 25 a normal urothelium, 24 cystitis and 20 urothelial
103 inflammation. In addition, for 27 BCPP participants in the control group, the urologist did not
104 provide a description apart from “no bladder cancer present” (Figure 1). All participants
105 received a baseline questionnaire including questions to assess demographic characteristics,
106 occupation and retrospectively characterise smoking and dietary behaviour.

107

108 **TNCO data from the UK Department of Health**

109 In the UK, an approved and accredited laboratory appointed by the UK Department of Health
110 periodically and independently analyses the yields of tar (T), nicotine (N) and carbon
111 monoxide (CO) in smoke of random samples of cigarette brands sold in the UK according to
112 the International Organisation for Standardisation (ISO) standards (Legislation UK 2002).
113 This examination verifies the TNCO yields declared on cigarette packs by manufacturers and
114 ensures that the TNCO yields of cigarettes on the UK market do not exceed the maximum
115 allowed levels as set out in the relevant Tobacco regulation (10 mg/cig for tar, 1 mg/cig for
116 nicotine and 10mg/cig for CO). This is a legal obligation in all Member States of the EU, and
117 is set out in the UK in the Tobacco Products (Manufacture, Presentation, Presentation and
118 Sale) (Safety) Regulations 2002 (Statutory Instrument 3041) (Legislation UK 2002). For tar,
119 measurements were made in line with ISO 4387 and for nicotine and CO, ISO 10315 and ISO
120 8454 were used respectively, with the accuracy of measurements determined by ISO 8243
121 (International Organization for Standardization (ISO)).

122 By combining these data with the filter cigarette brand(s) currently or previously
123 smoked in BCPP and the number of cigarettes smoked per day, daily intake of TNCO was
124 estimated. Intake is a proxy measure for absolute TNCO exposure, since it is an estimation of
125 the amount of TNCO that reaches the lungs which is also influenced by smoking behaviour
126 (e.g. puff volume and whether the cigarette is smoked completely). Patients who smoked
127 brands which were not in the UK Department of Health database were either excluded (88
128 out of 602, 15%) or the TNCO values were based on the original packaging as determined by
129 the manufacturer (40 out of 602, 7%).

130

131 **Statistical analysis**

132 From the BCPP questionnaire data daily TNCO intake was estimated through multiplying the
133 amount of cigarettes smoked per day (smoking intensity) with the TNCO levels. Based on
134 these TNCO levels, cigarettes were classified as either low tar/low nicotine (tar<9
135 mg/cigarette, nicotine <0.9 mg/cigarette) or high tar/high nicotine (tar≥9 mg/cigarette,
136 nicotine≥0.9 mg/cigarette). Odds ratios (OR) and 95% confidence intervals (CI) estimating
137 BC risk were calculated using logistic regression models. Potentially confounding factors
138 included in multivariate analyses were restricted to age, sex, and smoking duration. Ideally,
139 smoking intensity would also be included as a possible confounder but this was not possible
140 due to collinearity issues because smoking intensity is used to estimate daily TNCO intake.
141 Furthermore, data on occupation was sparse in controls (n=2 for controls, n=186 for NMIBC
142 cases) so occupational exposure could not be included as a covariate. Tests for linear dose-
143 response trends in ORs between TNCO intake categories were performed by comparing
144 logistic regression models with categorical variables for TNCO intake to models with a
145 continuous variable for TNCO intake by using likelihood-ratio (LR) tests.

146 **Results**

147 After exclusion of cases and controls in the analysis because of missing data on cigarette
148 brand or the number of cigarettes smoked per day 575 NMIBC, 139 MIBC and 130 BC-free
149 participants were included in the analysis. Figure 1 summarises the inclusion of participants
150 for this case-control study recruited from the BCPP participants. Table 1 shows the baseline
151 characteristics of the included NMIBC, MIBC and BC-free controls who were included in the
152 analysis.

153

154 Table 2 shows linearly increasing dose-response relationships between daily tar, nicotine and
155 CO intake and NMIBC risk compared to never smokers in both adjusted and unadjusted
156 models (p-values below 0.05 in all models). The adjusted logistic regression models show
157 mitigated associations compared to the unadjusted model. The highest OR was observed in
158 the highest intake category for tar (OR=3.00, 95%CI=1.36-6.63), although the 95%
159 confidence interval was wide.

160 The results were similar when looking at MIBC risk albeit the 95% confidence
161 intervals were wider due to the smaller number of MIBC cases (Table 3). Furthermore, the
162 only increasing trend in a multivariate model was observed for daily tar intake (p=0.046)
163 where the highest OR was 2.88 (95% CI=1.10-7.55).

164 Furthermore, there does not seem to be a meaningful difference in BC risk between
165 smokers of low tar/low nicotine cigarettes and smokers of high tar/high nicotine cigarettes
166 (p=0.544 for NMIBC and p=0.449 for MIBC). Additionally, smokers of low tar/low nicotine
167 cigarettes did not smoke more filter cigarettes than high tar/high nicotine cigarette smokers
168 on a daily basis (p=0.516, data not shown).

169 **Discussion**

170 This study is the first to investigate all TNCO levels from cigarettes in relation to BC risk
171 within a single study sample. Our results confirm the findings of another study, indicating a
172 linearly increasing dose-response relationship for daily tar and nicotine intake. Additionally,
173 we showed a similar association with daily CO intake (Zeegers et al. 2002). Another study
174 investigating cumulative tar intake did not show any association with BC risk (Castelao et al.
175 2001). Our results indicate that especially the highest daily intake categories of TNCO values
176 are associated with an increased risk of BC compared to the lower categories. Tar in cigarette
177 smoke is associated with cancer risk because of its high concentration of polycyclic aromatic
178 hydrocarbons (PAHs), oxidants and free radicals which all play an important role in inducing
179 DNA damage, possibly leading up to carcinogenesis (IARC 2010; Van Schooten et al. 1997).

180 The results might be driven by the number of cigarettes smoked and to a lesser extent
181 by TNCO values of cigarettes, since we did not observe any meaningful differences in BC
182 risk between smokers of low tar/low nicotine and high tar/high nicotine cigarettes. Although
183 this analysis was underpowered because of the low number of controls smoking low tar/low
184 nicotine cigarettes (n=7). Although smokers of low tar/low nicotine cigarettes did not smoke
185 more cigarettes than high tar/high nicotine cigarette smokers, they might have altered their
186 smoking behaviour (e.g. larger puff volume or more puffs) to increase nicotine intake
187 (Scherer 1999), as has been observed in other studies. Our estimates of daily TNCO intake
188 might be confounded by this compensation behaviour but could not be corrected for as
189 detailed smoking behaviour data was not collected.

190 Furthermore, the controls were selected from the BCPP cohort in which all
191 participants were under suspicion of bladder cancer at inclusion. Therefore, the control group
192 included individuals with chronic urothelial inflammation (Michaud 2007) and benign
193 papilloma (including some inverted papillomas) (Picozzi et al. 2013) which could be

194 considered risk factors for BC development. Hence, the presented ORs are probably
195 underestimated because the our control group is more similar to the case group than a
196 hypothetical, completely healthy control group because of the presence of these risk factors.

197

198 In conclusion, high daily intake of TNCO increases NMIBC risk compared to low daily
199 intake. However, it remains unclear whether smoking behaviour or cigarette type causes this
200 association. More research with larger sample sizes is needed to corroborate these results and
201 to shed light on whether smoking behaviour outplays cigarette content in determining BC
202 risk.

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268 **Figure 1. Flow chart of case and control selection from Bladder Cancer Prognosis**
269 **Programme**

270

271 **Table 1. Baseline characteristics of NMIBC cases, MIBC cases and BC-free controls**

272

273

274 **Table 2. Adjusted and unadjusted odds ratios (OR) estimating NMIBC risk for daily**
275 **tar, nicotine and CO intake and cigarette type comparing ever smokers to never**
276 **smokers.**

277

278

279 **Table 3. Adjusted and unadjusted odds ratios (OR) estimating MIBC risk for daily tar,**
280 **nicotine and CO intake and cigarette type comparing ever smokers to never smokers.**

281

282 **Table 1. Baseline characteristics of NMIBC cases, MIBC cases and BC-free controls**

	NMIBC (n=575)	MIBC (n=139)	BC-free (n=130)
Age at diagnosis (95% CI)	68.0 (67.1 - 68.8)	70.1 (68.2 - 71.9)	65.2 (63.0 - 67.5)
Sex (M/F)	442/133	99/40	91/39
Smoking status			
Never	127	31	59
Former	299	67	45
Current	149	41	26

283

284

411

412 **Table 2. Adjusted and unadjusted odds ratios (OR) estimating NMIBC risk for daily**
 413 **tar, nicotine and CO intake and cigarette type comparing ever smokers to never**
 414 **smokers.**

415

	Cases in cohort	Controls in cohort	OR (95% CI) crude	OR (95% CI) multivariate adjusted model*
Never smoker	127	59	1.00 (reference)	1.00 (reference)
Ever smoker	448	71	2.93 (1.97-4.36)	2.14 (1.11-4.11)
Tar (mg/day)				
<100	130	30	2.01 (1.22-3.33)	1.57 (0.78-3.15)
100-<200	154	21	3.41 (1.96-5.91)	2.73 (1.23-6.03)
>200	161	19	3.94 (2.23-6.94)	3.00 (1.36-6.63)
p-value for linear trend			<0.001	0.007
Nicotine (mg/day)				
<5	70	18	1.81 (0.99-3.30)	1.48 (0.69-3.18)
5-<10	93	16	2.70 (1.46-4.99)	2.02 (0.90-4.55)
10-<15	113	15	3.50 (1.88-6.51)	2.71 (1.15-6.41)
>15	169	21	3.74 (2.16-6.47)	2.85 (1.32-6.19)
p-value for linear trend			<0.001	0.030
CO (mg/day)				
<50	68	16	1.97 (1.06-3.69)	1.62 (0.73-3.56)
50-<100	71	14	2.36 (1.23-4.52)	1.69 (0.74-3.83)
100-<150	103	14	3.42 (1.81-6.47)	2.76 (1.15-6.61)
>150	203	26	3.63 (2.17-6.05)	2.75 (1.30-5.84)
p-value for linear trend			<0.001	0.034
Ever smoker cigarette type				
Low tar/low nicotine	52	7	3.45 (1.48-8.05)	2.80 (0.97-8.06)
High tar/high nicotine	396	64	2.87 (1.91-4.32)	2.14 (1.11-4.12)
p-value			0.667	0.544

*adjusted for age, sex and smoking duration

416
417

418 **Table 3. Adjusted and unadjusted odds ratios (OR) estimating MIBC risk for daily tar,**
 419 **nicotine and CO intake and cigarette type comparing ever smokers to never smokers.**

	Cases in cohort	Controls in cohort	OR (95% CI) crude	OR (95% CI) multivariate adjusted model*
Never smoker	31	59	1.00 (reference)	1.00 (reference)
Ever smoker	108	71	2.90 (1.71-4.91)	1.82 (0.79-4.21)
Tar (mg/day)				
<100	33	30	2.09 (1.08-4.04)	1.31 (0.52-3.28)
100-<200	28	21	2.54 (1.24-5.18)	1.42 (0.51-3.99)
>200	44	19	4.41 (2.21-8.80)	2.88 (1.10-7.55)
p-value for linear trend			>0.001	0.046
Nicotine (mg/day)				
<5	19	18	1.89 (0.92-4.37)	1.30 (0.48-3.50)
5-<10	19	16	2.26 (1.02-5.00)	1.26 (0.43-3.70)
10-<15	19	15	2.41 (1.08-5.39)	1.34 (0.43-4.20)
>15	48	21	4.35 (2.22-8.52)	2.75 (1.07-7.11)
p-value for linear trend			>0.001	0.105
CO (mg/day)				
<50	18	16	2.14 (0.96-4.77)	1.40 (0.51-3.83)
50-<100	17	14	2.31 (1.01-5.30)	1.19 (0.39-3.60)
100-<150	12	14	1.63 (0.67-3.95)	0.96 (0.29-3.16)
>150	58	26	4.25 (2.25-8.01)	2.60 (1.03-6.56)
p-value for linear trend			>0.001	0.061
Ever smoker cigarette type				
Low tar/low nicotine	13	7	3.53 (1.27-9.77)	2.69 (0.73-9.84)
High tar/high nicotine	95	64	2.83 (1.64-4.84)	1.80 (0.77-4.18)
p-value			0.265	0.449

*adjusted for age, sex and smoking duration

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