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

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Abstract

Objective

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

Methods

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

Results

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

Conclusion

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

Keywords: urinary bladder neoplasms; smoking; epidemiology; toxicology

Background

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

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

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

Methods

Study population

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

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

TNCO data from the UK Department of Health

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

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

Statistical analysis

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

Results

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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Table 2. Adjusted and unadjusted odds ratios (OR) estimating NMIBC risk for daily tar, 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	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

Table 3. Adjusted and unadjusted odds ratios (OR) estimating MIBC risk for daily tar, 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