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Research Article

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Urinary Thrombomodulin Levels Were Significantly Higher Following Occupational Exposure to Chemicals, In The Presence of Dipstick Protein, But Not in the Presence of Dipstick Blood

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Abstract

Currently, there are no biomarkers which can identify patients with an increased risk of developing urothelial cancer as a result of occupational chemical exposure. The aim of this study was to evaluate the relationships between final diagnosis and 22 biomarkers measured in urine, serum and plasma collected from 156 hematuric patients. Fourteen of the 80 patients (17.5%) with urothelial cancer and 13/76 (17.1%) of the controls were deemed to have a history of chemical exposure. We applied Fisher's exact tests to explore associations between chemical exposure and final diagnosis, and tumor stage and grade, where applicable; ANOVA and t-test to compare age across patients with and without chemical exposure; and Zelen's exact test to evaluate relationships across final diagnosis, chemical exposure and smoking. Following pre-selection of biomarkers using Lasso, we identified biomarkers with differential levels across patients with and without chemical exposure using Welch's t-test. Using a one-sided t-test and considering multiple testing using FDR, we observed that TM levels in urine were significantly higher in samples from patients with a history of chemical exposure regardless of their diagnosis as control or urothelial cancer (one-sided t-test, $p_{UC} = 0.014$ and $p_{CTL} = 0.043$); in the presence of dipstick protein and when urinary pH levels ≤ 6 ($p = 0.003$), but not in the presence of dipstick blood ($p = 0.115$). Urothelial cancer patients with a history of chemical exposure were significantly younger (64.1 years) than those without chemical exposure (70.2 years) (one-sided t-test p-value = 0.012); and their tumors were higher grade (Fisher's exact test; $p = 0.008$). There was a strong association between a history of chemical exposure and smoking in urothelial cancer patients (Zelen's exact test; $p = 0.025$). Elevated urinary thrombomodulin levels could have the potential to identify chemical exposure in hematuric patients at high risk of developing urothelial cancer.

Keywords: Thrombomodulin; Smoking; Bladder cancer; Urine; Chemical exposure; Occupation

Abbreviations: CE: Chemical Exposure; UC: Urothelial Cancer; NCE: No Chemical Exposure; CTL: Control; TURB: Trans Urethral Resection of the Bladder; FDR: False Detection Rate; ; CRP: C-reactive Protein; IL-4: Interleukin-4; TM: Thrombomodulin; MCP-1: Monocyte Chemo Attractant Protein 1; MMP9NGAL: Matrix Metalloproteinase Neutrophil Gelatinase Associated Lipocalin Complex; BPE: Benign Prostate Enlargement; MNI: Non- muscle Invasive; MI: Muscle Invasive

Introduction

Currently, there are no biomarkers which can identify patients who have an increased risk of developing UC as a result of occupational exposure to chemicals. Chemical exposure remains a significant risk factor for urothelial cancer (UC) in developed countries despite the laws which limit occupational exposure to harmful chemicals. This is attributable to both the latency periods that often exceed 20 years [1-3], and the significant range of chemical agents associated with increased risk of bladder cancer [3-7]. Recent evidence suggests that metal workers, car mechanics, plumbers [8], those exposed to intermediates in rubber and plastics manufacture [9], and those working in occupations allied to agriculture or medicine and health [10] could be at risk of developing UC. With respect to aromatic amines, risk is highest in those exposed at a younger age, those with over 10 years of exposure [11] and amongst certain categories of painters [12]. Polycyclic aromatic hydrocarbons

arising from incomplete combustion of carbon fuels can increase bladder cancer risk, e.g. in those exposed to diesel fumes [13] and amongst asphalt pavers [14]. Dermal absorption and inhalation of oils, fumes and metals may be one reason for the significantly increased risk of bladder cancer reported for employees who have worked for over 20 years on the assembly line in a car factory [15]. Smoking is regarded as the most significant risk factor for UC. Smokers are at least three times more likely to develop UC and their risk increases with increased pack-years of cigarette smoking [16,17]. However, the association between smoking and prognosis in patients diagnosed with UC is unclear [18].

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Material and Methods

Patients

One hundred and fifty-six patients with haematuria were recruited from Belfast City and Craigavon Area Hospitals to a case-control study, conducted according to Standards for the Reporting of Diagnostic accuracy studies guidelines, between November 2006 and October 2008. The study was approved by the Office for Research Ethics Committees Northern Ireland (ORECNI 80/04), reviewed by hospital review boards and registered (ISRCTN registry – 30128). The inclusion criteria were 1) patients with haematuria who have undergone cystoscopy; and 2) patients must be able to understand the study procedures and willing to give informed consent. The exclusion criteria were 1) patients who have not had a flexible cystoscopy; 2) patients who did not present with haematuria; 3) patients with UTI destined to undergo TURB; and 4) patients currently suffering from clinically evident alcoholism and or drug dependency. After written informed consent, a clean catch/mid-stream specimen of urine voided into a sterile collecting container (~50 ml), serum (2 ml) and plasma (2 ml) samples were collected from each patient and stored at -80°C until analysis [19]. Patients (98%) were recruited during normal working hours.

Chemical exposure

Occupations that were classed as high risk included painters [12], dye workers [20], foundry workers [7], hair dressers [21], lorry drivers [22], miners, metal workers, concierges and janitors [23]. Patients with no occupational risk and no known history of exposure to chemicals were assigned as “no chemical exposure” (NCE).

Biomarker analysis

Biomarker analyses (n = 22) in urine, serum and plasma were carried out as described previously. Briefly, scientists blinded to patient data, carried out the analysis of biomarkers at Randox Laboratories Ltd, County Antrim, Northern Ireland, using biochip array technology (BAT) (Randox Evidence © and Randox Investigator©) and ELISA, as previously reported. All analysis was carried out in triplicate (mean ± SD) [19].

Pathology diagnostic review

Following approval from the Northern Ireland Biobank (NIB13-0065), DOR (Consultant Pathologist), undertook a diagnostic review of 20 patients with UC; 12 who were assigned as CE and eight who were assigned as NCE.

Statistical analyses

We undertook the following analyses: Fisher's exact tests to explore the associations between CE, diagnosis and tumor stage and grade; ANOVA, prior to t-test, to investigate age within UC and control (CTL) subpopulations across CE and NCE; and Zelen's exact test [24] using the NSM3 R package [25] to explore the three way association across final diagnosis (UC vs CTL), chemical exposure (CE vs NCE) and smoking (non-smoker vs smoker).

Associations between biomarker levels and CE

We pre-selected biomarkers with non-zero coefficients using Lasso in conjunction with the glmnet function in the R package [26,27], and repeated the selection on 100 bootstrap datasets. The minimal λ (0.03636) was chosen by a 10 fold cross-validation procedure. Levels of the pre-selected biomarkers were \log_{10} transformed prior to analyses for differential levels across the CE and NCE subpopulations and across

dipstick urine analyses categories. We considered multiple testing applying the false discovery rate (FDR).

Results

Chemical risk across UC and control patients

Twenty-seven of the 156 patients (17%) were assigned as CE. Fourteen of these patients had UC (52%) with the following stages: pTa UC (n = 5), pT1 UC (n = 6), pT3a (n = 1), pT3b (n = 1) and pT4a (n = 1). Thirteen of these patients (48%) were CTLs. The occupational histories for the patients assigned as CE are detailed in Table 1.

Higher tumor grade in patients with a history of chemical exposure

Grade 1 (n = 4) and grade 2 tumors (n = 39) were combined (n = 43) for comparison to grade 3 tumors (n = 35). There was a significant association between grade and CE (Fisher's one sided exact test p = 0.008). The proportion of grade 1 and 2 tumors combined for NCE UC patients was 40/64 (63% (CI 51% to 74%)) in comparison to 3/14 (21% (CI 0% to 42%)) for CE UC patients; none of the UC patients with a history of chemical exposure had Grade 1 tumors (Table 2).

Younger age of UC patients with a history of chemical exposure

UC patients with a history of CE were significantly younger (median = 64 years (IQR 59 to 71)) than NCE UC patients (median = 71 years (IQR 65 to 76)) (ANOVA; p < 0.001) (t-test; p = 0.012). Further, there was no statistically significant difference in age when CE CTL and NCE CTL patients were compared; both groups had an average age of 54 years (Table 2).

The relationship between CE and smoking across controls and UC patients

The proportion of patients with CE who also smoked (13/14, 93%) was significantly higher in the UC subpopulation in comparison to the CTL subpopulation (4/13, 31%) (p=0.00122). The odds ratios of UC patients with CE who also smoked (odds ratio = 5.18) were higher in comparison to the odds ratio in the CTL subpopulation (odds ratio = 0.32) (p = 0.025, Zelen's test). It is noteworthy that the associations of smoking and CE were not significant when assessed independently for CTL (p1=0.062) and UC (p2=0.08) patients.

Biomarkers with differential expression across CE vs NCE patients

Four urinary biomarkers, i.e. C-reactive protein (CRP), interleukin-4 (IL-4), Thrombomodulin (TM), and IL-2 together with plasma biomarkers, monocyte chemo attractant protein 1 (MCP-1) and matrix metalloproteinase neutrophil gelatinase associated lipocalin complex (MMP9NGAL) were pre-selected using Lasso. Urinary IL-2, and the two plasma biomarkers, MCP-1 and MMP9NGAL, were less stable (bootstrap ≤ 0.11) than the three urinary biomarkers TM, CRP and IL-4 (bootstrap ≥ 0.34). Urinary TM was the only biomarker that was differentially expressed across the NCE and CE subpopulations (mean NCE = 4.5 ng/ml; mean CE = 6.8 ng/ml) (Welch's t-test; p = 0.002). Further, urinary TM was significantly higher in CE patients across both subpopulations, i.e. UC (mean NCE = 4.5 ng/ml; mean CE = 7.1 ng/ml) (one-sided t-test; p = 0.014) versus CTL (mean NCE = 4.5 ng/ml; mean CE = 6.2 ng/ml) (one-sided t-test; p = 0.043) groups demonstrating that the differential expression was independent of UC.

Diagnosis	Present Occupation	Past occupation(s)
UC	Timber yard – painter / sprayer	Supervisor - Hardware Store
UC	Retired	Car painter
UC	Retired	Marine engineer
UC	Retired	Landscape contractor
UC	Retired	Lorry driver/agricultural sprayer
UC	Engineering-mechanical	Engineer
UC	Retired	Process operator - car manufacture
UC	Retired	Fireman
UC	Production worker	
UC	Retired	Lorry driver
UC	Retired	Service engineer
UC	Retired	Mechanical engineer
UC	Unemployed	Cable joiner
UC	Retired	School caretaker/ tyre making
control	Retired	Road service maintenance
control	Retired	Building - skilled labourer
control	Retired	Foreman – works ministry
control	Window blind fitter	Fabric factory – mixed dye
control	Retired	Newspaper - production photographer
control	Recreation park - attendant	Coal man
control	Taxi driver	Moulding factory
control	Retired	Carpet cleaner
control	Clergyman	TV technician/ RAF radio inspector
control	Joiner	
control	Warehouse	Plastics manufacturer
control	Lorry driver	Car mechanic/car valeting
control	Retired	Labourer

Each patient's occupational history was reviewed by three authors (MR, CR and KW) and assigned low risk (score 1), moderate risk (score 2), or high risk (score 3). Scores were averaged. Patients deemed to have an occupational history associated with a high risk of bladder cancer; or patients reporting that they had been exposed to chemicals, passive smoking, weed-killers, dyes, paints, leather, metal, rubber, vehicle oils/fumes or other described carcinogens were assigned as CE.

Table 1: Occupational histories for CE patients.

Thrombomodulin levels were higher in patients with a history of chemical exposure

Using a one-sided t-test and considering multiple testing using FDR, we observed that TM levels in urine were significantly higher in CE patients, in the presence of dipstick protein and when urinary pH levels ≤ 6 ($p = 0.003$), but not in the presence of dipstick blood ($p = 0.115$). TM levels corrected using creatinine ($p = 0.029$) were significantly higher in patients with a history of chemical exposure. TM and creatinine levels measured in urine were significantly correlated (Pearson correlation; $r = 0.72$, $p < 0.001$). For the remaining biomarkers $r = < 0.5$ (Pearson correlation).

Micropapillary variant of UC in patients with a history of chemical exposure

Interestingly, there were features of the micropapillary variant of UC [28] in the four biopsies available for review from 3 patients with a history of CE. The first biopsy from one of these patients was a pT2G1 tumor which displayed micropapillary features. Further, micropapillary and nested patterns were observed in the recurrence from the same

	CTL		UC		Total(% cohort)
	NCE	CE	NCE	CE	
	63	13	66	14	
Age					
Age (mean (SD))	54.3 (19.1)	54.1 (16.7)	70.2 (8.1)**	64.1 (8.4)*	
Final diagnosis					
	(% column)	(% column)	(% column)	(% column)	
No diagnosis	27 (42.9)	9 (69.2)	0	0	36 (37.5)
Benign pathologies	5 (7.9)	1 (7.7)	0	0	6 (3.8)
Stones and inflammation	15 (23.8)	1 (7.7)	0	0	16 (10.3)
BPE	10 (15.9)	2 (15.4)	0	0	12 (7.7)
Other cancers	6 (9.5)	0	0	0	6 (4.2)
NMI UC	0	0	51 (77.3)	11 (78.6)	62 (39.7)
MI UC	0	0	15 (22.7)	3 (21.4)	18 (11.5)
Grade 1/2 UC			40 (62.5)	3 (21.4)	43 (27.5)
Grade 3 UC			24 (37.5)	11 (78.5)**	35 (22.4)**
Dipstick blood					
-ve	23 (36.5)	5 (38.5)	12 (18.2)	3 (21.4)	43 (25.6)
+	13 (20.6)	5 (38.5)	24 (36.4)	2 (14.3)	44 (28.2)
++	9 (14.3)	0	4 (6.0)	1 (7.1)	14 (9.0)
+++	17 (27.0)	3 (23.0)	22 (33.3)	5 (35.7)	47 (30.1)
++++	1 (1.6)	0	4 (6.0)	3 (21.4)	8 (5.0)
Smoking					
Smokers	37 (58.7)	4 (30.8)	47 (71.2)	13 (92.9)	101 (64.7)
Smoking years (mean (SD))	26.0 (16.2)	21.3 (8.5)	35.4 (14.5)	37.4 (9.6)	N/A
TM (ng/ml) (mean)	4.5	6.2***	4.5	7.1***	

*UC patients with CE were significantly younger than UC patients with NCE. **UC patients with CE had higher grade tumors than UC patients with NCE. ***patients with CE had significantly higher levels of urinary TM than NCE patients.

Table 2: Patient characteristics (n = 156).

patient which was reviewed as a pT2G3. Carcinoma *in situ* (CIS) and lymphovascular invasion were observed in 3/4 (75%) biopsies [29] with micropapillary features (Figure 1). Notably these three patients had smoked for more than 10 years. Eight of the 12 CE patients (66%) had recurrences, four of which were higher grade/stage disease (Table 3).

There was no evidence of micropapillary features in the biopsies from the eight patients with NCE and no recurrences were recorded for these patients. However, 2/8 (25%) of these patients had tumors which displayed a nested pattern (Table 4).

Discussion

TM is a glycoprotein expressed on the surface of endothelial cells, on the membranes of the transitional epithelium and in the cytoplasmic region of umbrella cells [30]. Positive TM immunoreactivity has been shown to have an inverse correlation with cancer progression and metastasis [31,32]. Previously, we reported that the immunodetection of cytoplasmic membrane-bound TM in UC, squamous cell carcinoma and adenocarcinoma formalin fixed paraffin embedded tissue microarrays was independent of grade and stage. Furthermore, TM immunostaining was significantly stronger in the UC tissue sections with respect

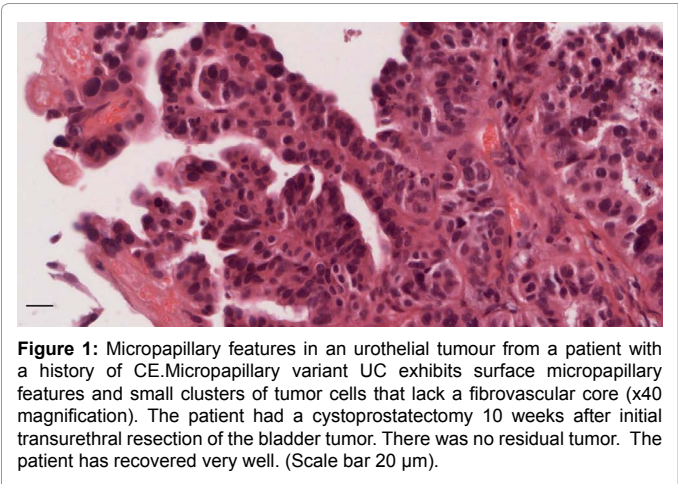


Figure 1: Micropapillary features in a urothelial tumour from a patient with a history of CE. Micropapillary variant UC exhibits surface micropapillary features and small clusters of tumor cells that lack a fibrovascular core (x40 magnification). The patient had a cystoprostatectomy 10 weeks after initial transurethral resection of the bladder tumor. There was no residual tumor. The patient has recovered very well. (Scale bar 20 μ m).

to both adenocarcinoma and SCC sections which stained weakly [33]. TM expression has also been shown to be increased in the transitional epithelium in patients with cystitis [32].

Although increased levels of plasma TM are considered to reflect endothelial damage [34], the physiological significance of soluble TM in UC is unknown [35]. TM is shed into the circulation following its proteolytic cleavage from endothelial surfaces and increased TM levels have been associated with endothelial dysfunction [36]. Endothelial shedding is common in patients with hypertension, hypercholesterolemia, diabetes, atherosclerotic disease, and in chronic smokers [35,37]. Further, TM has anti-inflammatory properties and is known to increase during inflammatory conditions [38]. It is therefore conceivable that by-products from CE could potentially induce endothelial shedding or irritation within the bladder which could result in an increased level of urinary TM.

While health and safety regulations may limit occupational exposure to harmful chemicals, related cases of bladder cancer remain high as the latency period for cancer development after exposure may be as long as 20 years [20]. Similarly to our findings of aggressive UC tumors in those exposed of chemicals, Noon et al. [20] reported that patients exposed to crack detection dye penetrants normally present with high-grade tumors with associated panurothelial carcinogenesis, in contrast to most UC which are unifocal and low grade.

In our study, urinary TM was the only biomarker that was differentially expressed across the NCE and the CE subpopulations. Urinary TM levels were significantly higher in CE patients, in the presence of dipstick protein, but not in the presence of dipstick blood. Furthermore, UC patients with a history of both smoking and CE tended to have more aggressive tumours, and at a significantly younger age, in comparison to UC patients with no history of CE.

There is a need for new approaches to identify patients who are at risk of serious disease. Urinary TM may be a novel biomarker that could be used to screen patients in potentially 'at risk' occupations. Where levels of urinary TM levels are found to be elevated, further investigations are warranted. It should be noted that our study is limited by the small numbers of patients in each of the groups and our conclusions should be viewed in this context. As such, a larger study is required to validate our findings.

Acknowledgements

Patient	Age	Smoking years	Grade	Stage	Inflammation	Pattern	CIS	LVI
1	>60*	<10	2 #	TA	3	sessile	absent	no
			2	TA	0	papillary	absent	no
			3	TA	0	papillary	present	no
2	>60*	>10	2	TA	0	papillary	absent	no
			2	TA	2	papillary	absent	no
3	>60*	>10	1 #	TA	0	papillary	absent	no
			2	TA	0	papillary	absent	no
4	>60	>10	2 #	TA	0	papillary	absent	no
			3	T1	2	papillary	present	yes
5	>60	>10	3	T1	1	micro-papillary	present	yes
6	<60	>10	3	T4A	1	nested	absent	yes
7	>60	>10	3	T2	1	micro-papillary	present	yes
			3	T2	3	micro-papillary and nested	present	yes
8	<60	>10	0		0	papillary	absent	no
			3	TA	0	papillary	absent	no
9	<60	>10	0 #	TA	0	papillary	absent	no
			1	TA	1	papillary	absent	no
			3	TA	3	papillary	absent	no
10	>60	0	3	T2	1	nested	absent	no
			3	T2	1	squamous diff	absent	no
11	<60	>10	3	TA	1	micro-papillary	absent	no
12	<60	>10	2	TA	0	papillary	absent	no

Table 3: Pathological review of 22 biopsies from 12 UC patients with CE. Following approval from the Northern Ireland Biobank (NIB13-0065), DOR (Consultant Pathologist), undertook a diagnostic review of all tumor biopsies that were available within the Belfast City Hospital archive for each of the 12 patients with UC who were assigned as CE. Eight of the 12 (66%) patients with a history of CE had recurrences, four of which were higher grade/stage disease #. INF inflammation: 0 absent, 1 = +, 2 = ++, 3 = +++; LVI lymphovascular invasion*patients with incomplete biomarker data who were not included in the biomarker analyses

Patient	Age	Smoking years	Grade	Stage	Inflammation	Pattern	CIS	LVI
1	<60	0	3	T1	1	nested	present	no
2	>60	>10	CIS	TIS	1	CIS	present	no
3	>60	0	3	T2	1	papillary	absent	no
4	>60	0	3	T1	1	papillary	present	no
5	>60	>10	3	TA	2	papillary	absent	no
6	>60	>10	2	TA	0	papillary	absent	no
7	>60	>10	3	T1	2	papillary	present	no
8	>60	>10	3	T3A	1	nested	present	yes

Table 4: Pathological review of 8 tumors from 8 UC patients with NCE. Following approval from the Northern Ireland Biobank (NIB13-0065), DOR (Consultant Pathologist), undertook a diagnostic review of all tumor biopsies that were available within the Belfast City Hospital archive for each of 8 patients with UC who were assigned as NCE.No recurrences were recorded for the eight NCE patients.INF inflammation: 0 absent, 1 = +, 2 = ++, 3 = +++; LVI lymphovascular invasion

MWR and CNR are employees of Randox Laboratories Ltd who undertook the biomarker analyses using multianalyte biochip array technology. RdMS, FES, BD, MWR, CNR and KEW have been or will be named on patents: 1. Methods for the detection of, or risk of, bladder cancer (JWJ01571US January 2013 and JWJ01571GB August 2009). 2. A method of defining the likelihood of a subject

having bladder cancer JWW01839GB October 2012. 3. A method for detecting exposure to a hazardous chemical JWW01877GB (on going). Randox Laboratories Ltd paid the salary of Mr Funso Abogunrin who recruited the patients over two years. Invest Northern Ireland RD0412515 funded RdMS and GC.

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