Early Results of Urothelial Carcinoma Screening in a Risk Population of Coke Workers: Urothelial Carcinoma among Coke Workers

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Objective To present the protocol and the early results of a urothelial carcinoma (UC) screening analysis performed in a risk population of coke workers. **Methods** Between June 2006 and October 2008, 171 male workers (mean age 43 years), employed in a Ligurian coke plant (Italiana Coke S.r.l) and exposed to polycyclic aromatic hydrocarbons (PAHs) for a median period of 16 years, underwent screening for UC. Urological evaluation included medical history, physical examination, routine laboratory tests, urine analysis, urinary cytology and uCyt+ assay. In the event of signs and symptoms suggestive of UC or positive urinary tests, the workers were also subjected to urinary ultrasonography and cystoscopy with biopsy of any suspicious lesions. **Results** Regarding the laboratory tests, 19/171 (11%) uCyt+ samples were considered inadequate and were excluded from the outcomes assessment. Overall, urine analysis, cytology and uCyt+ were positive in 18/152 (12%) subjects who showed no evidence of UC at the scheduled check-ups. No significant association was identified between marker positivity and occupational activity. **Conclusions** Our results fail to show an increased risk of UC among the coke workers evaluated. However, they will need to be confirmed in the future by a larger enrollment and a longer follow-up in order to assess the definitive risk for UC after exposure to coke.

Key words: Bladder cancer; Screening; Occupation; Risk factor; Urinary markers

INTRODUCTION

The association between exposure to selected carcinogens and urothelial carcinoma (UC) is well established and it is estimated that 20%-27% of bladder cancers are attributable to occupational exposures[1-2]. Historically, the most consistently identified at-risk industries are polycyclic aromatic hydrocarbon (PAH) manufacturers. Moreover, high exposure to PAH mixtures have been reported in several occupations, including coal gasification, diesel engine exhausts, iron, steel foundries, coke, coal tar, carbon black, and carbon electrodes productions[3-4].

The epidemiological evidence from workers occupationally exposed to PAHs has been reviewed by the International Agency for Research on Cancer (IARC), which classifies some industries as carcinogenic to humans, mainly due to an increased risk of lung, laryngeal, skin, kidney, and urinary bladder cancer[5]. Furthermore, many researchers have focused on the risk of UC stemming from the occupational exposure not only of compound carcinogenicity but also on exposure intensity, workplace characteristics and individual susceptibility to this form of cancer[6-7].

Based on these aspects, in the last few years, the detection of people at risk of UC has been taken into particular consideration by urologists and many screening protocols have been performed producing lots of papers addressing the association between occupational factors and UC[7-11].

The aim of this study is to present the protocol and the early results of a UC screening analysis performed in a population of coke workers employed in a Ligurian coke plant.

MATERIAL AND METHODS

In the period between June 2006 and October 2008, 171 male workers (mean age 43 years, ranging between 22 and 57 years) employed in a Ligurian coke plant (Italiana Coke S.r.l) underwent, during the scheduled medical visit, a screening for UC by the

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same expert urologist. This population was considered at risk of UC due to the chronic exposure to PAHs formed during coke production[6-8]. In particular, the mean period of worker exposure to the risk factors was 16 years (range 1-36 years). Table 1 shows the specific occupational activities.

Patient urological evaluation included medical history, physical examination, routine laboratory tests, urine analysis, urinary cytology, and uCyt+ assay. In the event of signs and symptoms suggestive of UC or positive urine analysis, urinary cytology and uCyt+ assay results, patients underwent urinary ultrasonography and cystoscopy with biopsy of any suspicious lesions. Patients' characteristics and associated further risk factors for UC are reported in Tables 2 and 3.

Urine Analysis, Cytology and uCyt+ Staining.

Voided urine (40 to 80 mL) samples were collected from workers and evaluated by urine analysis (Combur-9 Roche, Basel, Switzerland), liquid-based cytology (ThinPrep, Cytyc, Boxborough, Mass) and uCyt+ assay (Diagnocure, Quebec, Canada). Urine analysis results were either "negative" or "positive" for microhaematuria. As regards cytology, specimens negative for malignancy or with atypia of any degree were categorized as "negative" while specimens considered suspicious or positive for malignancy as "positive"[12]. The Ucyt+ test was performed using a fluorescence microscope (Provis AX 70 Olympus, Italy) with filters for fluorescein and Texas red emission light detection. Red fluorescence revealed cells positive for high-molecular-weight glycosylated carcino-embryogenic antigen, and green fluorescence revealed cells positive for bladder cancer mucins. The samples were considered positive when they showed at least one green or one red fluorescent cell. Any slide with less than 500 cells was considered inadequate for the validation of a negative result. The results obtained using fluorescence microscopy were correlated with morphology, as recommended by the manufacturer[13].

The results assessment was performed after collecting clinical, laboratory, and instrumental data including ultrasonographic, cystoscopic, and histological data, collected in the event of suspect UC. According to Cohen's effect size conventions, the power of statistical analysis was 0.80. Data were analyzed using SPSS®.

RESULTS

All 171 workers completed the screening protocol. The medical history, routine laboratory tests, and physical examination results were substantially unexpressive except for an abnormal DRE and a mild increase in total PSA value reported in 3/171 (2%) and 1/171 (0.6%) workers respectively, who were sent to our urological outpatient department for further tests (Table 2).

As concerns the specific risk evaluation for UC, besides occupational exposure, all subjects reported at least another associated risk factor. In particular, 56/171 (33%) were strong smokers, 62/171 (36%) lived near the industrial site, and 1/171 (0.6%) reported a previous superficial bladder tumor (Table 3).

Regarding the laboratory tests, urine analysis and cytology were evaluable in all workers while 19/171 (11%) uCyt+ samples were considered inadequate and excluded from the outcomes assessment.

Finally, 152 subjects were analysed. Urine analysis, cytology and uCyt+ were positive in 3/152 (2%), 6/152 (4%), and 12/152 (8%) subjects respectively. Notably, the 3 workers with positive urine analyses also reported positive uCyt+ results while no other cases of double positivity for the urinary tests was assessed. No significant association was identified between marker positivity and occupational activity.

Overall, 18/152 (12%) workers who reported positive for at least one urinary marker underwent ultrasonography and cystoscopy. The ultrasonography reported no evidence of UC in all cases while the cystoscopy demonstrated a lesion suspicious for UC in 7 subjects who underwent biopsy with an eventual diagnosis of benign bladder tissue (Fig. 1).

Based on these data the false positive rate for urine analysis, cytology and uCyt+ was 2%, 4%, and 8% corresponding to a specificity of 98%, 96%, and 92% respectively.

DISCUSSION

Several excellent reviews of the epidemiological evidence which links selected chemical, occupations, and industries to UC are reported in literature[6-8]. Particularly, over 40 different occupations and more than 200 chemicals, mainly represented by PAHs, have been identified as risk factors for UC[5]. To date, the surveillance of risk populations has become an appreciable part of the urological workload and many authors published their data concerning the screening for UC in high risk population groups, reporting positive effects on patients' morbidity and mortality and on the costs of the healthcare system[9-11,14-15]. In the present study, we report our early experience concerning the development of UC in a risk group of workers, employed in a Ligurian coke plant, who were exposed to the products formed during coke production for a mean period of 16 years.

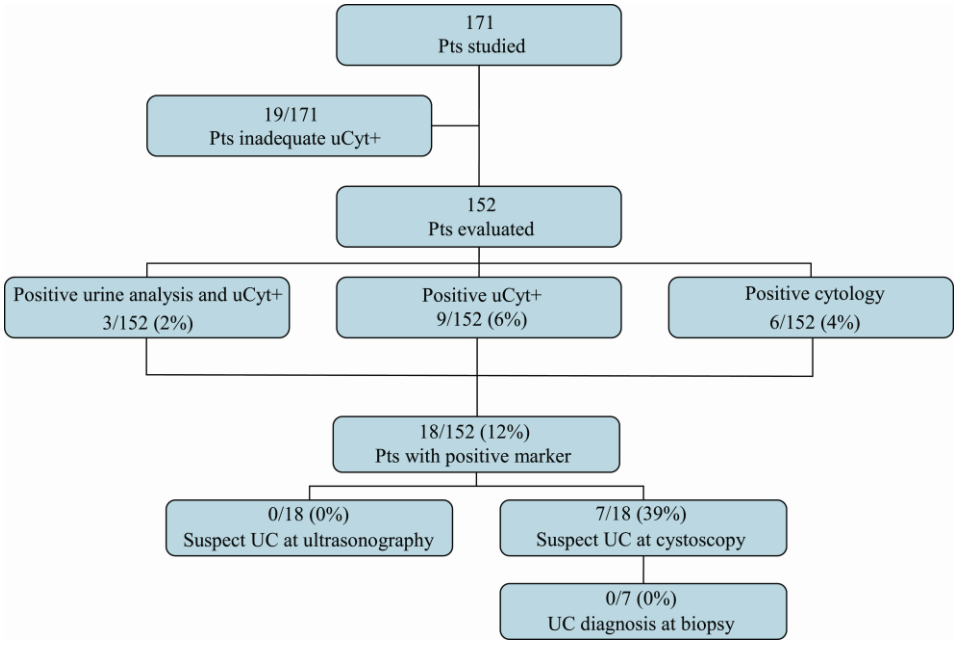

FIG 1. Flow chart concerning patient data and results. Pts=patients; UC=urinary cancer.

In accordance with other authors, our screening protocol also included an extensive history and physical examination, in order to identify possible associated risk factors or suspect lesions for UC, followed by non-invasive urinary tests which could help to distinguish healthy individuals from those who required further examination such as cystoscopy, urography or CT scan[9-11,16-17]. Particularly, we decided to combine the execution of urine analysis with urinary cytology and the uCyt+ assay in order to produce a high detection rate for all forms of UC, limiting the need for cystoscopy only in the event of a positive urine analysis[18-22].

Based on this protocol, the evaluated history for all 152 workers showed further risk factors for UC, but no clinical suspect of UC. Overall, urine analysis, cytology and uCyt+ assay indicated a suspect of UC in 18 out of 152 subjects (12%) who underwent ultrasonography and cystoscopy with biopsy, reporting no diagnosis of UC. Furthermore, no significant association was identified between marker positivity and occupational activity.

These results failed to show an increased risk of UC after chronic exposure to coke products. In fact, this aspect has already been discussed in literature by other authors.

Boffetta *et al*., who reported a systematic review up to 1997 on occupational exposure to PAHs, and showed no evidence of an increased risk of bladder cancer with reference to coke production[23]. On the contrary, Bye *et al*. reported an excess risk of UC in relation to the cumulative dose of PAHs[24]. However, in the following years, Bosetti *et al*., interpreted with caution the results by Bye due to the small number of patients and the short follow-up, and confirmed no general evidence of increased risk of UC among coke workers[8].

Although our outcomes seem to match comparatively well with those reported by the above mentioned authors, some considerations should be taken with regard to these data. The papers reported in literature are generally mortality retrospective studies, probably related to the invasive forms of UC, which can cause death, and not to the superficial UCs which are most frequent and often indolent[8,23-24]. Thus, these data could not correspond to the real risk for UC after coke exposure which needed to be clarified by specific prospective trials, based on a wider urological evaluation, targeted on the detection of all forms of UC. In this setting, our study protocol, which is based on a prospective urological evaluation, could provide new and interesting data concerning this topic. However, our outcomes are also limited by some factors. Firstly, the number of workers enrolled is rather small for a risk evaluation study and is insufficient to allow an extensive statistical analysis concerning the influence of the different risk factors in the development of UC among coke workers. Secondly, the analysis is based on only one assessment and no follow-up observation is available; further evaluations could allow assessment not only of the specificity and false positive rates but also of the sensitivity and false negative rates of the urine markers used in order to verify the real effectiveness

of this screening protocol. Thirdly, the mean period of exposure to PAHs is rather short. In fact, with respect to the latency of UC, most studies have found that the occupational risk to develop a cancer is rarely increased before at least 20 years from the onset of exposure[25-26].

Based on these considerations, we think that the risk of UC after esposure to coke needs to be clarified by further prospective studies which include a urological schedule. Our results, although derived from a correct urological assessment, are still too partial and preliminary to assess the definitive risk for UC after coke exposure and should be confirmed in the future after a larger enrolment and a longer follow-up.

CONCLUSION

The outcome of our screening analysis does not report diagnosis of UC among the coke workers evaluated. These results, which seem to confirm that there is no increased risk of UC after chronic coke exposure, are not supported in literature by many prospective trials concerning the specific risk of development of UC in coke production and need to be confirmed in the future by a larger enrolment and a longer follow-up.

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Competing interests

I certify that all competing interests, including specific financial interests and relationship and affiliations relevant to the subject matter or materials discussed in the manuscript are the following: Claudio Giberti and Antonio Genova are consultants for Italiana Coke Industry S.r.l. Fabrizio Gallo and Maurizio Schenone have nothing to disclose.

TABLE 1

Workers' Occupational Activity in the Coke Plant

Workers' occupational activity	**N °**
Coke Oven	93 (54%)
Coke Products	44 (26%)
Coke Oven Maintenance	27 (16%)
Laboratory	7 (4%)
Total	171 (100%)

TABLE 2

Patients' Characteristics Concerning Medical History, Laboratory Tests and Physical Examination

Patients' characteristics	
Number of Patients	171
Mean Age (Years-range)	43 (22-57)
Mean Period of Exposure to PAHs (Years-range)	16 (1-36)
BSM Exposure Level	< 1.6 mg/m^3
Hereditary Urothelial Neoplasm (N °pts -%)	2/171 (1%)
Previous Urological Non-neoplastic Diseases (N °pts -%-)	17/171 (10%) 4 Prostatitis 8 Urolithiasis 2 Varicocele 3 Fimosis
Alcohol Intake (≥ 50 mL/daily) (N °pts -%-)	68/171 (40%)
Coffee Intake (≥ 3 cups/ daily) (N °pts -%-)	151/171 (88%)
LUTS (No pts -%-)	18/171 (11%)
Abnormal DRE (No pts -%-)	3/171 (2%)
Mean Total PSA (ng/mL) (Range)	0.9 (0.06-4.6)
Concomitant Urological Non-neoplastic Diseases (No pts -%-)	8/171 (5%) 3 Epididymal Cysts 3 Varicocele 1 Hydrocele 1 Inguinal Hernia

Note. PAHs=polycyclic aromatic hydrocarbons; LUTS=lower urinary tract symptoms; DRE=digital rectal examination. PSA=prostatic specific antigen

TABLE 3

Associated Risk Factors for UC among the 171 Patients Evaluated

Associated risk factors for UC	**Number of pts (%)**
Tobacco Smoking (≥ 15 Cigarettes/daily)	56/171 (33%)
Home Near Job Area (2 kms)	62/171 (36%)
Previous form of UC	1/171 (0.6%)
Chronic Urinary Tract Infection	0/171 (0%)
Previous EBRT for Pelvic Tumors	0/171 (0%)
Previous CT	0/171 (0%)

Note. EBRT=external beam radiotherapy; CT=chemotherapy

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