THE CYTOLOGICAL EVALUATION OF BLADDER AND LUNG CARCINOMA RATES ON THE WORKERS EXPOSED TO INDUSTRIAL CHEMICALS

Endüstriyel kimyasallara maruz kalan işçilerde mesane ve akciğer kanser oranlarının sitolojik incelemeyle değerlendirilmesi

Serpil OĞUZTÜZÜN[1], Mehtap AYDIN[2], Z.Aytül ÇAKMAK[3], Murat KILIÇ[1], Ümit YIRTICI[1], Meral ATAY[4], Müzeyyen ÖZHAVZALI[5], Erdal YILMAZ[6], Emine Ö.KARAASLAN[7]

[1]Kırıkkale Üniversitesi, Biyoloji Bölümü, KIRIKKALE
[2]Sanatoryum Eğitim ve Araştırma Hastanesi, Patoloji Bölümü, ANKARA
[3]Kırıkkale Üniversitesi, Tıp Fakültesi, Halk Sağlığı ABD, KIRIKKALE
[4]Hannover Cytology Institute, GERMANY
[5]Kırıkkale Üniversitesi, Matematik Bölümü, KIRIKKALE
[6] Kırıkkale Üniversitesi, Tıp Fakültesi, Üroloji ABD, KIRIKKALE
[7]Kırıkkale Üniversitesi, Kimya Bölümü, KIRIKKALE

Geliş Tarihi: 13.02.2009
Kabul Tarihi: 02.09.2009

İletişim:
Serpil OĞUZTÜZÜN
Kırıkkale Üniversitesi,
Fen Fakültesi, Biyoloji Bölümü,
71450 Yahşihan, KIRIKKALE

Tel : +90 318 357 4242-1508
Fax : +90 318 357 24 61
E-posta : soguztuzun@yahoo.com

ÖZET

Amaç: Bu çalışmanın amacı, Kırıkkale'de endüstriyel kimyasallara maruz kalan işçilerin, mesane ve akciğer kanseri oranlarının idrar ve balgam sitolojisi yöntemleri uygulanarak değerlendirilmesidir.

Yöntem: Barut fabrikasında çalışan 123 işçinin idrar sitolojisi örnekleri, ağır silah ve çelik, silah ve mühimmat fabrikalarında çalışan 408 işçinin balgam sitoloji örnekleri Papanicolaou yöntemiyle hazırlanmış ve ışık mikroskobunda değerlendirilmiştir.

Bulgular: 123 işçiden 15'inin idrarında atipik sitolojik bulgular görülmüştür. Bu işçilerin hiçbirinde önceden mesane kanseri hikâyesi belirlenememiş ve ultrasonlarında da anormal bulgular görülmemiştir. 408 işçinin 209'u nun balgam sitoloji uygunsuz materyal nedeniyle değerlendirmeye alınamamıştır. Kalan 199 işçiden 103'ünde normal sitoloji, 33'ünde skuamoz metaplazi, 2'sinde displazi belirlenirken, 61 işçide de inflamasyon görülmüştür. İşçilerin kimyasallara maruziyet süresi ve sitoloji bulguları arasında bilimsel olarak anlamlı bir ilişki bulunamamıştır ($p>0.05$). Günde 20 adetten fazla sigara içenlerde anormal balgam (%1,2) ve idrar (%13) sitoloji bulguları saptanmasına karşın istatistiksel olarak yalnızca balgam sitolojisi sonuçlarıyla sigara alışkanlığı arasında bir kolerasyon bulunmuştur ($p=0.015<0.05$).

Sonuç: Sitolojik yöntemlerin uygulanmasının kolay ve ucuz olması ayrıca veinvaziv işlemlere gerek duyulmaması nedeniyle özellikle mesane ve akciğer kanserinin erken tanısında ve kitle taramalarında faydalı bir yöntem olarak kullanılabileceği düşünülmektedir.

Anahtar Sözcükler: İdrar sitolojisi, balgam sitolojisi, tarama, kimyasal karsinojenler, erken teşhis, mesleki maruziyet.

ABSTRACT

Objective: The aim of this study is to evaluate the ratios of bladder and lung carcinomas of workers exposed to industrial chemicals in Kırıkkale, Turkey by urinary and sputum cytology methods.

Method: Urinary cytology preparations for a total of 123 workers in the gun powder production plant and sputum cytology preparations for a total of 408 workers in the heavy gun and steel, gun, and ammunition plants were prepared using Papanicolaou staining and evaluated by light microscopy.

Results: For the cytological diagnoses of voided urine in all 123 workers, 15 workers had atypical cytological findings. None of them had a prior history of bladder cancer and no significant abnormality was found in their ultrasound examinations. Regarding the cytologic diagnoses of sputum in 408 workers, 209 individuals could not be evaluated because of

inappropriate materials. Of the remaining 199 workers, 103 of them had results within normal limits while 33 of them showed squamous metaplasia, 2 dysplasia and 61 inflammations. No statistically significant relatedness could be found between the workers' exposure time to chemicals and the cytological findings ($p>0.05$). Although abnormal cytological findings of sputum (1.2%) and urine (13%) was found for the smokers of more than 20 cigarettes a day, a statistical correllation was determined between only sputum cytology results and smoking habits ($p=0.015<0.05$).

Conclusion: Because of Cytological methods being easy to apply and relatively inexpensive in addition to not requiring invasive operations, these methods can be used especially for monitoring and early detection of human bladder and lung carcinomas.

Key Words: Urine cytology, sputum cytology, screening, chemical carcinogens, early diagnosis, occupational **exposure**

INTRODUCTION

Urine cytology is regarded as a valuable screening method for the detection of preclinical bladder cancer among workers in the British dyestuffs industry (1). Detection of a developing bladder cancer before the onset of symptoms offers opportunities for earlier intervention and, possibly, an improved outcome (1).

The most important known risk factor for bladder cancer in North America and Europe is smoking which increases the risk two to five fold and which may be responsible for as many as 50% of all cases (2). Bladder cancer has long been recognized as an occupation-related cancer. It has been estimated that as much as 20% of bladder cancer cases could be attributable to occupational carcinogens (3). There are several known and suspected occupational bladder carcinogens, some of which have been recognized for many decades. Most notable among these are 2-naphthylamine and benzidine, which have been associated with relative risks among highly exposed workers (4). Excess risks of bladder cancer have been documented with cohort studies from several industries: magenta or auramine manufacturing, the rubber industry, aluminum production, and coal gasification. However, some of these industries have been transformed or virtually eliminated, and it is not clear whether substantial risks of occupational bladder cancer remain (5).

Sputum screening for lung cancer is an area that has been significantly researched by different groups. Saccomanno and coworkers (6) collected sputum samples from workers in uranium mines deemed to be at high risk for developing lung cancer. Their sputum was found to harbour atypical cells and patients with these abnormalities overtime developed lung cancer. The link between abnormal sputum cytology and lung cancer development has been subsequently confirmed in other studies (7-9).

Due to expansion of industrialization and urbanization, the prevalence of respiratory disorders has been increased. Occupational respiratory disorders have been recognized for centuries (10,11). Industrial dust, smoke and fumes and poor working environment have been recognized as important causative factors in increasing the prevalence of lung carcinoma among industrial workers. Age, smoking habit, duration and type of exposure at working sites, nutritional and socio-economic status, etc. are known contributory factors (12,13).

The present article reports on a study of cytological monitoring of sputum and urine in workers exposed to chemicals such as ethyl acetate, ethyl alcohol, isopropyl alcohol, thinner, ether, hydrochloric acid, sulphiric acid, diethyl ether, lead, lead vapor, benzene, nitrotoluene, 2,4-dinitrotoluene, 2,4,

6-trinitrotoluene, nitroglycerin, nitrocellulose, carbon black, asbestos in the heavy gun and steel, gun, gunpowder production and ammunition plants in Kırıkkale, Turkey. It is well known that some of above mentioned chemicals are among important carcinogens, and they have strong toxicity (14-30).

MATERIAL AND METHODS

In this study, urine samples from 123 workers at the gun powder plant and 408 workers at the heavy gun and steel, gun, and ammunition plants who were exposed the chemicals such as ethyl acetate, ethyl alcohol, isopropyl alcohol, thinner, ether, hydrochloric acid, sulphiric acid, diethyl ether, lead, lead vapor, benzene, nitrotoluene, 2,4-dinitrotoluene, 2,4, 6-trinitrotoluene, nitroglycerin, nitrocellulose, carbon black, asbestos were searched by cytological examination. The ages of workers range between 28-58 years. All are male. Their smoking habits were also searched by questionnaire.

The gunpowder production plant in Kırıkkale, Turkey, manufactures and processes carcinogenic chemicals. The 123 workers were exposed to toxic chemicals at various stages were examined for urine cytology. A screening program for early diagnosis of bladder cancer was organized for those workers who were identified and persuaded to participate in this study. In total, 123 voided urines were prefixed by adding equal volumes of 50% ethanol to the specimens. They were prepared using the membrane filter method of 123 and Papanicolaou staining. All cytology specimens were evaluated by a pathologist (M. Atay from Hannover Cytology Clinic, Germany). The cytological diagnoses classified each specimen as “Positive”, “Suspicious”, “Atypical” or “Negative”. The “positive” category was for nuclear abnormalities for the diagnosis of cancer (31). “Suspicious” indicated similar changes that were suggestive but for some reason (e.g., paucity of cells), were not conclusive for cancer. “Atypical” indicated qualitatively similar but lesser nuclear abnormalities, below the level of cancer. “Negative” indicated only normal urothelial cells or non-neoplastic abnormalities.

A total of 408 workers in the heavy gun, steel, gun and ammunition plants who were exposed to the toxic chemicals were examined for sputum cyctology. For each sputum examination, four cytological slides were prepared. The smears were stained by the Papanicolaou technique. The slides were screened and evaluated independently by a pathologist (M. Aydın from Sanatorium Education and Research Hospital, Ankara, Turkey) as not appropriate for diagnosis, normal, squamous metaplasia, dysplasia (32). For data analysis, the sputum cytology diagnoses were first categorized into five groups: (a) inappropriate specimen (containing no informative bronchial epithelial cells and macrophage cells), (b) normal (negative), (c) inflammation, (d) squamous metaplasia, and (e) dysplasia.

The statistical relationships between workers’ cytological diagnosis and their smoking status and the time of exposure to toxic and carcinogenic chemicals were examined by Kendal Tau c test for checking whether they were in concordance or not.

RESULTS

Qualitative modifications (cellular changes, inflammatory infiltrate, metaplasia and dysplasia) in the urine of 123 workers, occupationally exposed to toxic chemicals, were evaluated. The 103 of them were negative, 5 of them were inflammation and 15 of them were atypical cases. The 65 workers exposed to chemicals for less than 15 years had 55 negative, 2 inflammation and 8 atypical cases. Moreover, 58 workers exposed to chemicals for more than 15 years had 48 negative, 3 inflammation and 7 atypical cases (Table 1).

The 96 smokers of 123 urine cytology, 79 had normal transitional epithelia, 5 had inflammatory

cells, erythrocytes and metaplasia, and 12 had atypical changes (Figure 1-3) However, in the cytological examination of 27 non-smokers, 24 samples were normal and 3 samples showed atypical urothelial epithelia (Table 1).

Statistically the urine cytology results are not correlated with the duration of exposure (p=0.812) and smoking habits (p=0.571) according to Kendall's tau c and Kappa Tests.

For monitoring and possible early diagnosis, further investigation was realized by ultrasound. The 15 subjects with atypical cytology had no significant abnormalities as observed by ultrasound.

According to the sputum cytological results, out of 199 workers, 103 had results within normal limits, 33 had squamous metaplasia while 2 persons had dysplasia, and 61 persons had inflammation (Figures 3-6).

The 136 workers who were exposed to chemicals for less than 15 years had the following cases: 72 negative, 39 inflammations, 24 metaplasias and one dysplasia. Moreover, 63 workers who were exposed to chemicals for more than 15 years had the following cases: 31 negative, 22 inflammations, 9 metaplasia and one dysplasia (Table 2).

Out of 161 smokers, 77 had normal cytology, 52 had inflammation, 30 had metaplasia, and 2 had dysplasia in their sputum cytology. However, out of 38 non-smokers, 26 had normal cytology, 9 had inflammation, and 3 had metaplasia (Table 2).

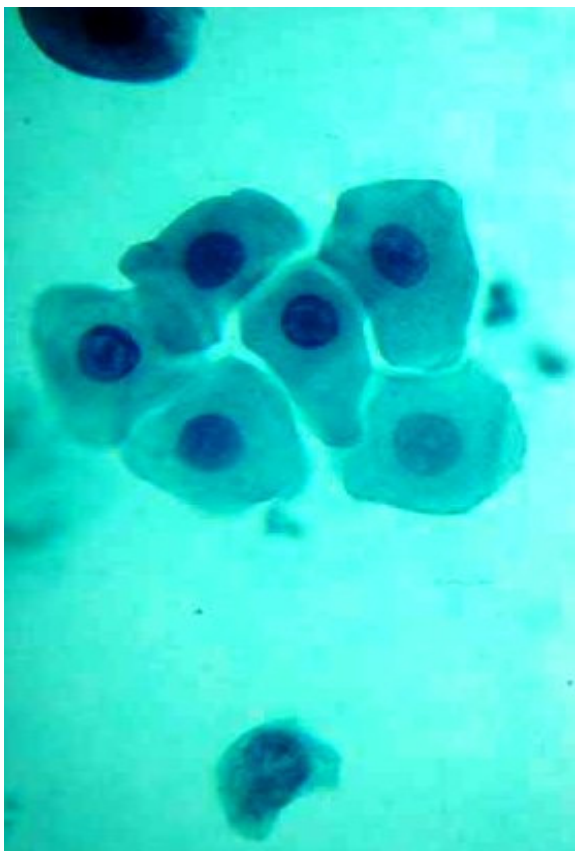

Figure 1. Sqamous cell metaplasia in urine cytology. Metaplasia cells have hyperchromatic nucleus (PAP, x200).

Table 1. Duration of exposure to chemicals, smoking status and urinary cytological diagnosis of workers at the gun powder production plant in Kırıkkale.

		Cytological diagnosis			
		Negative	**Inflammation**	**Atypical**	**Total**
Exposure to chemicals	≤15 years	55	2	8	65
	>16 years	48	3	7	58
Total		**103**	**5**	**15**	**123**
Smoking status	Non-smokers	24	-	3	27
	<20 pcs/day	19	3	5	27
	>20 pcs/day	60	2	7	69
Total		**103**	**5**	**15**	**123**

Statistically the sputum cytology results were not correlated with the duration of exposure (p=0.737) and but correlated with smoking habits (p=0.015<0.05) according to Kendall's tau c and Kappa Tests.

DISCUSSION

Since the initial report of Crabbe and coworkers (1), many cohorts of high-risk industrial workers have been studied with cytological methods. The ability of cytological screening to ultimately improve the clinical outcome of occupational bladder cancer has been debated (33-35). Both industrial screening and follow-up of known tumors confirmed that urine cytology could detect important but occult lesions, particularly non-papillary carcinoma in situ (CIS) and associated small infiltrating carcinomas. Cytology also detected several lesser atypias in flat urothelium, below the level of CIS (36-40).

Figure 2. Atypical or dysplastic cells in urine cytology. (PAP, x200)

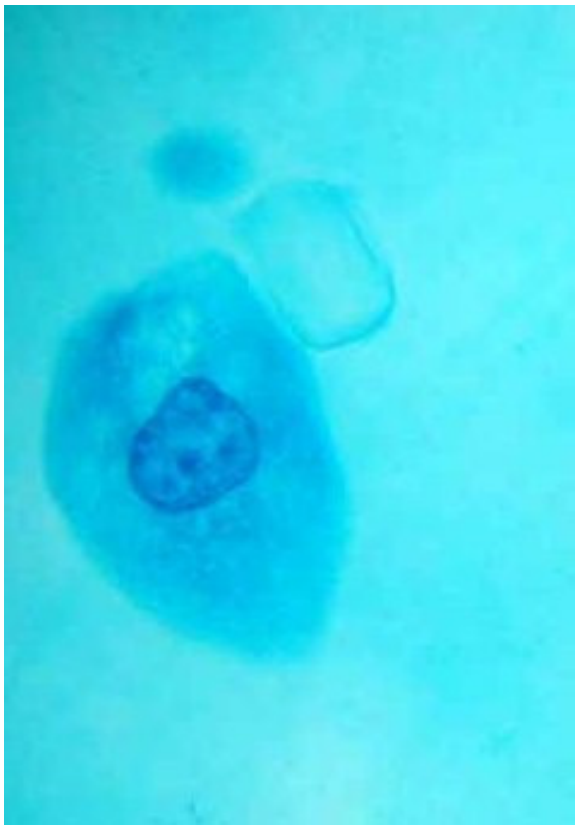

Figure 3. Atypical or dysplastic cells in urine cytology. They have nucleolus and high nucleus/cytoplasm ratio (PAP, x400)

Table 2. Duration of exposure to chemicals, smoking status and sputum cytological diagnosis of workers at the gun powder production plant in Kırıkkale.

		Cytological diagnosis				
		Negative	**Inflammation**	**Atypical**	**Dysplasia**	**Total**
Exposure to chemicals	≤15 years	31	22	9	1	63
	>16 years	72	39	24	1	136
Total		**103**	**61**	**33**	**2**	**199**
Smoking status	Non-smokers	26	9	3	-	38
	<20 pcs/day	40	20	10	-	70
	>20 pcs/day	37	32	20	2	91
Total		**103**	**61**	**33**	**2**	**199**

The incidence of urothelial and renal cancer cases found in miners exposed to explosives containing dinitrotoluenes (DNT) was increased by a factor of 4.5 and 14.3, respectively (41). Morbidity of total malignant tumors in males was markedly higher in Chinese trinitrotoluene (TNT) factory workers than controls (relative risk, 2.3; ref. 42). Puntoni and coworkers (43) investigated the frequency of lung and bladder cancers in a group of 2286 longshoremen employed at the Geneva dockyard who were exposed occupationally to carbon-black dust. They identified 208 cancers, 53 lung cancers and 32 bladder cancers. They founded that the longshoremen who were exposed to high concentrations of carbon black had a significantly increased frequency of bladder cancer.

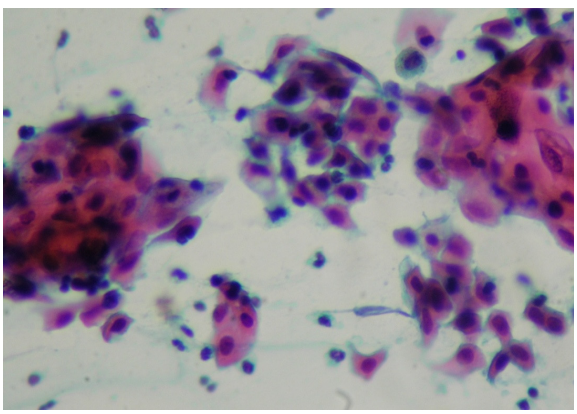

Figure 3. Hyperchromatic squamous metaplasia cell groups in sputum. (PAP, x200)

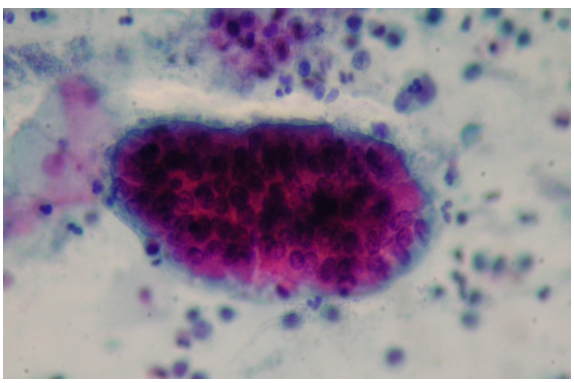

Figure 4. Bronchiolar hyperplasia cell grous in sputum (PAP, x200)

Glashan and coworkers considered mild atypia to be the earliest detectable abnormality in developing industrial bladder cancer (37).

In the present study, 123 workers in the gunpowder factory, occupationally exposed to toxic chemicals, were evaluated by urine cytology. The 65 workers who had been exposed to chemicals for less than 15 years had 2 inflammation and 8 atypical cases. Moreover, 58 workers who had been exposed to chemicals for more than 15 years had 3 inflammation and 7 atypical cases. In addition, the 96 smokers of 123 urine cytology, 5 had inflammatory cells, eritrocytes

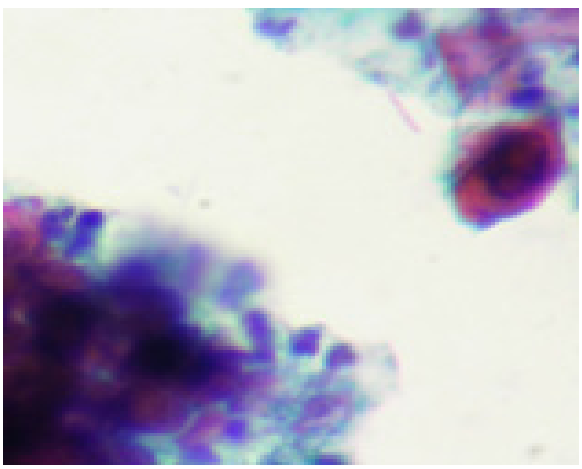

Figure 5. Dysplastic cell with high nucleus/cytoplasm ratio in sputum (PAP, x400)

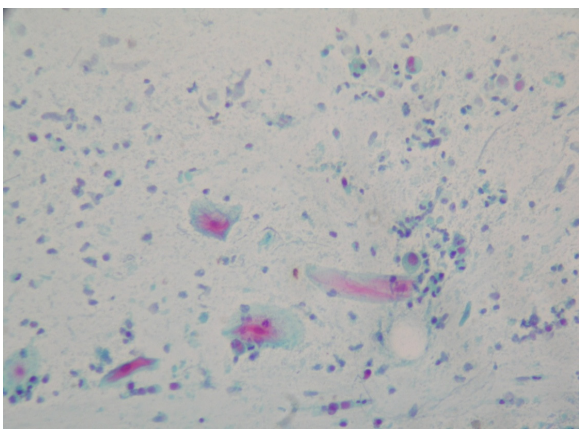

Figure 6. Inflammatory case from sputum (PAP, x100)

and metaplasia, and 12 had atypical changes. However, in the cytological examination of 27 non-smokers, 3 samples were showed atypic urothelial epithelia. Although we found that the smokers had 5 inflammation and 12 atypia cases, while non-smokers had 3 atypia cases, statistically, the results were not correlated with time of exposure and smoking habits ($p>0.05$). We conclude that a larger sample size should be used for this kind of monitoring.

The diagnostic yield of sputum cytology is known to vary in relation to tumor location. Its greatest use is in the identification of central tumors, and it is of little or no value in the identification of peripheral cancers (44).

The workers in the gunpowder factory under study had exposure to a variety of irritants and smoke containing gunpowder, carbon monoxide, thinner, carbon particles, metal fumes from lead, oxides of iron and nitrogen, aldehydes, sulfur dioxide, hydrogen chloride etc. They cause widespread bronchial narrowing by directly injuring the airway mucosa and inflammatory swelling and excessive secretions and/or by stimulating rapidly adapting irritant receptors (45).

There have been several estimates of the proportion of male lung cancers that are due to occupational exposures. Recent estimates of 9% (46) and 3-17% (47) have come from large case-control studies and refer to the proportion of lung cancers attributable to work in occupations with excess risk of lung cancer, rather than to lung cancer attributable to specific occupational carcinogens (48).

Rodriguez and coworkers (49) examined the risk of lung cancer among workers in the main industrial processes of a large iron and steel foundry in Asturias, Spain. They found that workers having ever been employed in the blast furnace had an excess lung cancer risk compared to a reference group of workers not employed in metal producing departments. In addition, they indicated that tobacco smoking appeared to be an important positive or negative confounder for subgroups of workers.

According to the sputum cytological results of the present study, out of 199 workers, 33 had squamous metaplasia while 2 persons had dysplasia, and 61 persons had inflammation. Out of 161 smokers, 52 had inflammation, 30 had metaplasia, and 2 had dysplasia in their sputum cytology. However, out of 38 non-smokers, 9 had inflammation, and 3 had metaplasia. The 136 workers who had been exposed to chemicals for less than 15 years had 39 inflammations, 24 metaplasias and one dysplasia cases. Moreover, 63 workers who had been exposed to chemicals more than 15 years had 22 inflammations, 9 metaplasia and 1 dysplasia cases. Statistically the sputum cytology results were not correlated with the duration of exposure ($p= 0.737$) and but they were correlated with smoking habits of workers ($p=0.015<0.05$).

It can be concluded that exposure to toxic chemicals, tobacco smoking, can all contribute to pathogenesis of respiratory disorders. Using protective devices, discouraging smoking, conducting engineering measures to create a safe working environment and periodical health checks for workers are recommended measures to reduce respiratory disability among workers.

Environmental carcinogenesis in various forms is likely to remain for a long time. In future, long-term observation of this study will offer a chance to study developing human bladder cancer prospectively with these routine methods in tandem with new approaches, for example, fluoresence in situ hybridisation (FISH) for diagnosis and prognosis.

REFERENCES

1. Crabbe JGS. Exfoliative cytological control in occupational cancer of the bladder. Br. Med. J. 1952; 2:1072-76.
2. International Agency for Research on Cancer. Tobacco smoking. IARC Monogr Eval Carcinog Risk Chem Hum 1986; 38.
3. Vineis P, Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. Arch Environ Health 1991; 46:6-15.
4. Case RAM, Hosker ME, McDonald DB, et al. Tumors of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. I. The role of aniline, benzidine, alphanaphthylamine and beta-naphthylamine. Br. J. Ind Med 1954; 11:75-104.
5. Case RAM, Hosker ME. Tumor of the urinary bladder as an occupational disease in the rubber industry in England and Wales. Br. J. Prev. Soc Med. 1954; 8:39-50.
6. Saccomanno G, Archer VE, Auerbach O, et al. Development of carcinoma of the lung as reflected in exfoliated cells. Cancer 1974; 33:256-70.
7. Prindiville SA, Byers T, Hirsch FR, et al. Sputum cytological atypia as a predictor of incident lung cancer in a cohort of heavy smokers with airflow obstruction. Cancer Epidemiology, Biomarkers and Prevention 2003; 12:987-93.
8. Tockman MS, Gupta PK, Myers JD, Frost JK, Baylin SB, Gold EB, et al. Sensitive and specific monoclonal antibody recognition of human lung cancer antigen on preserved sputum cells: a new approach to early lung cancer detection. J Clin Oncol 1988; 6:1685-93.
9. Risse EK, Vooijs GP, van't Hof MA. Diagnostic significance of 'severe dysplasia' in sputum cytology. Acta Cytol 1988;32: 629-34.
10. Bates D.V. Air pollutants and the human lung, Am. Rev. Respir Dis; 1972; 105:1.
11. Parkes W.R. Occupational Lung Disorders, London, Butterworths, 1974.
12. Viswanathan R, Modi R, Prasad S. and Singh S.I. Bronchial Asthma and Chronic Bronchitis. J. Ind. Med. Assoc, 1965; 45:480.
13. Roland H. Ingram (Jr.) In Harrison's Principles of Internal Medicine, llth ed. McGraw Hill Book Company; 1987, 1087.
14. Akrill, P, Guiver R, Cocker, J. Biological monitoring of nitroglycerin exposure by urine analysis. Toxicology letters 2002; 134(1-3): 271-6.
15. Sabbioni, G. Rumler, R. Biomonitoring of workers cleaning up ammunition waste sites. Biomarkers 2007; 12(6): 559-73.
16. Sabbioni G, Liu Yu-Y, Yan H and Sepai O. Hemoglobin adducts, urinary metabolites and health effects in 2, 4, 6-trinitrotoluen exposed workers. Carcinogenesis 2005; 26, 7: 1272-9.
17. Sabbioni G, et al. Comparison of biomarkers in workers exposed to 2, 4, 6-trinitrotoluene. Biomarkers 2007; 12(1):21-37.
18. Sabbioni G, et al. Biomarkers of exposure, effect, and susceptibility in workers exposed to nitrotoluenes. Cancer Epidemiol Biomarkers Prev 2006; 15(3): 559-66.
19. Tchounwou PB, et al. Environmental toxicology and health effects associated with dinitrotoluene exposure. Reviews on Environmental Health; 2003; 18(3): 203-29.
20. Withers RMJ, Lees FP. The lethal toxicity of bromine. Journal of Hazardous Materials 1987; 14(2): 274-5.
21. Humsan, Kaj, Kuopio R. Symptomps of car painters with long term exposure to a mixture of organic solvents. Scandiniavian Journal of Work Environment and Health 1980; 6(6)1: 19-32.
22. Huang, W-Y, Lian H-Q. Study of occupational experience of workers exposed to organic solvents and its effective factors.. Xiandai Yufang Yixue 2005; 32(6): 611-2.
23. Alekperov II, et al. Hygienic and toxicological evaluation of labor conditions and state of health of workers in the production of isopropyl alcohol. Azerbaidzhanskii Meditsinskii Zhurnal 1981; 58(8): 44-9.
24. Takeuchi, Y. Hisanaga, N. Ono, Y. Ogawa, T. Hamaguchi, Y. Cerebellar dysfunction caused by sniffing of toluene-containing thinner. Industrial Health 1981; 19(3): 163-9.
25. Steenland K, Schnorr T. Beaumont J, Halperin W, Bloom T. Incidence of laryngeal cancer and exposure to acid mists. British Journal of Industrial Medicine 1998; 45(11): 766-76
26. Ida S, Yokato M, Yoshioka H, Takiguchi Y. Single exposure to gasoline or ether reduces cytochrome p-450 activities without affecting UDP-glucuronosyltransferase activity in rat liver. Journal of Occupational Health 2000;42(2): 84-5
27. Salandova J, et al. Health state of persons occupationaly exposed to diethyl ether and ethyl alcohol. Pracovni Lekarstvi 1990; 42(8): 337-40.
28. Buchet JP, Roels H, Bernard A, Jr Lauwerys R. Assessment of renal function of workers exposed to inorganic lead, cadmium or mercury vapor. Journal of Occupational Medicine 1980; 22(11): 741-50.

29. Puntoni R, Ceppi M, Reggiardo G, Merlo F. Occupational exposure to carbon black and risk of bladder cancer. The Lancet 2001; 358:562.

30. Jex TT and Wyman DO A Minireview of benzene. Toxic substance mechanisms, 1996; 15:135-43.

31. Koss LG. Diagnostic Cytology and its histopathologic Bases. Third edition. Philadelphia, JB Lippincott, 1979; 711-817.

32. Kennedy TC, Proudfoot, SP, Franklin, WA, Merrick, TA, Saccomanno, G, Corkill, M E, Mumma, DL, Sirgi, KE, Miller, YE, Archer, PG, and Prochazka, A. Cytopathological analysis of sputum in patients with airflow obstruction and significant smoking histories. Cancer Res., 1996; 56: 4673-8.

33. Davies JM, Parkes HG. Benefits of cytological screening for bladder cancer. Acta Cytol 1982; 26:98.

34. Fox AJ, White GC. Bladder cancer in rubber workers. Lancet 1976; 1:1009-1011.

35. Koss LG. Environmental carcinogens and cytology. Acta Cytol 1980; 24:281-2.

36. Forni A, Ghetti G, Armeli G. Urinary cytology in workers exposed to carcinogenic aromatic amines: A six-year study. Acta Cytol 1972; 16:142-5.

37. Glashan RW, Wijesinghe DP, Riley A. The early changes in the development of bladder cancer in patients exposed to known industrial carcinogens. Br. J Urol 1981; 53:571-7.

38. Koss LG, Melamed MR, Kelly RE. Further cytological and histologic studies of bladder lesions in workers exposed to para-aminodiphenyl: Progress report. J Natl Cancer Inst 1969; 43:233-43.

39. Reichborn-Kjennerud S, Hoeg K. The value of urine cytology in the diagnosis of recurrent bladder tumors. Acta Cytol 1972; 16:269-72.

40. Murphy WM, Irving CC. The cellular features of developing carcinoma in murine urinary bladder. Cancer 1981; 47:514-22.

41. Brüning T, Chronz C, Their R, Havelka J, Ko Y, Bolt HM. Occurrence of urinary tract tumors in miners highly exposed to dinitrotoluene. J. Occup Environ Med 1999;41:144-9.

42. Yan C, Wang Y, Xia B, Li L, Zhang Y, Liu Y. The retrospective survey of malignant tumor in weapon workers exposed to 2, 4, 6-trinitrotoluene. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2002; 20: 184-8.

43. Puntoni R, Ceppi M, Reggiardo G, Merio F. Occupational exposure to carbon black and risk of bladder cancer. Lancet 2001;358:562.

44. Thunnissen FBJM. Sputum examination for early detection of lung cancer. J Clin. Pathol. 2003; 56: 805-10.

45. Bates D.V. Air pollutants and the human lung, Am. Rev. Respir Dis. 1972;105:1.

46. Morabia A, Markowitz S, Garibaldi K, Wynder E. Lung cancer and occupation: Results of a multicentre case-control study. Br J Ind Med 1992;49:721-7.

47. Vineis P, Thomas T, Hayes R, Blot W, Mason T, Pickle L, Lorrea P. Proportion of lung cancers in males due to occupation in different areas of the U.S. Int J Can 1988;42:851-6.

48. Steenland K, Loomis D, Shy C, Simonsen N. Review of occupational lung carcinogens. Am J of Ind Med 1996; 29:474-90.

49. Rodriguez V, Tardon A, Kogevinas M, Prieto CS et al. Lung cancer risk in iron and steel foundry workers: a nested case control study in Asturias, Spain. Am J of Ind Med 2000; 38: 644-50.