British Journal of Industrial Medicine 1981;**38**:240-246

A case-control study of bladder cancer in the United States rubber and tyre industry

H CHECKOWAY,[1] A H SMITH,[3] A J McMICHAEL,[4] F S JONES,[5] R R MONSON,[2] AND H A TYROLER[1]

From the Occupational Health Studies Group,[1] School of Public Health, University of North Carolina, Chapel Hill, NC 27514, and Department of Epidemiology,[2] Harvard School of Public Health, Boston, MA 02115, USA

ABSTRACT A case-control study of bladder cancer was conducted in five United States rubber and tyre companies to determine if there were high-risk jobs and work areas within the industry. The study included 220 male cases of bladder cancer, of whom 107 were identified from hospital record reviews and 113 from death certificates. Each case was matched individually with two industry controls by sex, race, year of birth, and company. One control was matched additionally by year of hire and duration of employment. Comparisons of cases and controls not matched by year of hire and age of hire showed no differences for those variables, which suggests that age and calendar period of first exposure to the industry were not risk determinants. When the work histories of both cases and controls were contrasted it was found that cases were more likely than controls to have worked in milling (odds ratio (OR) = 1·91) and calender operation (OR = 2·21) jobs. The relative risk estimates for milling and calender operation both exhibited linear trends of increase with duration of exposure. Milling and calender operation jobs entail potential exposures to volatilised reaction products from heated rubber stock. A better understanding of aetiological associations with job type will require more detailed characterisation of the work environment with regard to the sources and levels of aromatic amines and other suspected bladder carcinogens.

An increased risk of bladder cancer among rubber and tyre manufacturing workers has been reported during the past three decades from epidemiological investigations in Britain and the United States. Case and Hosker[1] and Veys[2] showed an excess of deaths from bladder cancer in the British rubber manufacturing industry. Findings from these studies contributed to the identification of the specific bladder carcinogens, beta-napthylamine and benzidine. In Veys's study[2] a cumulative incidence of 10% was found among a historic cohort followed for 35 years. Confirmatory evidence has come from investigations by Cole *et al*[3] and by Mancuso and El-Attar[4] in the United States, and by Fox and Collier[5] in England.

In 1970 the United Rubber, Cork, Linoleum, and Plastic Workers International Union and six United States rubber companies agreed to support a comprehensive programme of research into occupationally related diseases. A series of cohort mortality studies was conducted in which the mortality experience of rubber workers in five major companies was contrasted with mortality in the United States population. Monson and Nakano[6] reported a standardised mortality ratio (SMR) of 122 (22% excess of observed to expected deaths) for bladder cancer among white male workers from one company for the years 1940-74. They also observed greater than expected bladder cancer mortality among female workers (SMR = 189); however, this was based on only seven deaths.[7] McMichael *et al*[8] computed an SMR of 92 for bladder cancers for white male workers from four companies for the period 1964-73.

Current addresses: Department of Community Health,[3] Wellington Clinical School of Medicine, Wellington 2, New Zealand, Division of Human Nutrition,[4] CSIRO, Adelaide, S Australia, and Department of Preventive Medicine,[5] Lovelace-Bataan Medical Center, Albequerque, NM 87108, USA.

Received 29 July 1980
Accepted 9 September 1980

We report the findings of a case-control study of bladder cancer conducted within the same five United States tyre and rubber manufacturing companies surveyed in the mortality studies.[6–8] Despite the failure to detect an industry-wide excess of deaths from bladder cancer, it was considered important to determine whether there may have been high-risk work environments within the industry. Accordingly, the work histories of bladder cancer cases and controls, drawn from the rubber industry, were compared to discover potential occupational hazards.

Methods

STUDY SUBJECTS

All the study subjects were hourly paid production workers employed at the largest plant of one of the five rubber companies. All five companies are located in Akron, Ohio. Cases of bladder cancer were identified from two sources.

The first was a hospital record review of all bladder cancers newly diagnosed during the years 1958-74 in the four major Akron area hospitals. (These data were initially collected by Guira[9] as part of a clinically based study seeking evidence of increased bladder cancer frequency among rubber production workers.) Cases among rubber workers were identified by means of cross-checking the hospital record listings against the lists of hourly paid employees of the five companies. Table 1 gives descriptions of the employee lists and their years of coverage. Of the cases identified from the hospital records, only subjects meeting the following criteria were included in the study: (1) the tumour was first diagnosed at one of the four Akron area hospitals during the years 1954-74; (2) an original pathology report or microscopic surgical slide was available to document bladder cancer; (3) the bladder tumour was not an adenocarcinoma or an undifferentiated carcinoma also affecting the prostate; and (4) the case had no previous history of colonic or cervical cancer.

The second source of cases was death certificates obtained for the mortality studies. The years of death certificate screening were: 1964-73 for companies A, D, and E; 1950-73 for company C; and 1940-74 for company B. The death certificates were classified for cause of death by a nosologist from the

Table 1 *Rubber worker employee list descriptions*

Company	*Years of coverage*	*Source*	*Estimated No of workers in cohort*
A	1965-74	All workers since 1964 and some pre-1965 personnel cards	5 000
B	1940-74	All workers who worked at least 5 years (computer files)	20 500
C	1950-73	Computer file of all personnel	33 000
D	1945-75	All personnel cards for workers active since 1945	20 000
E	1910-75	All personnel cards since company's founding	20 000

Table 2 *Description of occupational title groups in rubber and tyre manufacturing*

Occupational title group	*Description*
1 Batch preparation	Natural and synthetic rubbers, accelerators, antioxidants, etc, are weighed and mixed in a Banbury mixer
2 Milling	Rubber mix from the Banbury is processed further under heat and pressure until rubber is in a soft plastic state
3 Calender operation	Rubber stock from mill is rolled out into sheet of controlled thickness
4 Plystock handling	Rolled rubber (plystock) is cut and spliced
5 Extrusion	Rubber stock from mill is forced through a die and is extruded as tread rubber or tube stock. This strip is cut into appropriate lengths and cut ends are cemented
6 Fabrication-tyres, beads	Beads are rubber and fabric-covered wires that rest on wheel rim. Treads, beads, and plystock are used to build tyre
7 Tubes	Inside of tube from extruder is coated with talc, cut, spliced together, and valves are attached
8 Curing preparation	Assembled uncured or green tyre or tube is inspected, repaired, and coated with antisticking agents
9 Curing	Green tyre or tube is placed in mould and vulcanised under heat and pressure
10 Final inspection-tyres	Cured tyre is trimmed, inspected, and labelled for shipping
11 Maintenance	This OTG includes mechanics, pipe-fitters, electricians, welders, painters and millwrights
12 General service	All operations associated with power plant, quality control, trucking, and janitorial service
13 Shipping and receiving	Activities associated with receiving, unloading, and storing incoming materials; loading final product into trucks and box cars
14 Reclaim	Scrapped, vulcanised rubber products are shredded and devulcanised. Rubber compound is restored to its original plastic state by milling
15 Chemicals	Chemical products, including synthetic latex are compounded, mixed, dried, and bagged
16 Plastics	Jobs in this OTG include manufacturing of foam, urethane, and vinyl products
17 Preparation non-tube and tyre	Raw ingredients for other rubber products are compounded and mixed before Banbury milling
18 Final inspection-tubes	Cured tube is inspected, patched and buffed, and made ready for shipping
19 Metal products	Raw steel is cleaned in a pickling tank before being shaped and welded. Rims are major metal product
20 Special products	Includes manufacturing of rubber and non-rubber products such as footwear, adhesives, and fuel cells
21 Unknown	Jobs for which there is not enough information on the work history to assign to a specific OTG

National Center for Health Statistics. Individuals for whom bladder cancer (ICDA code 181 by the 7th revision, 188 by the 8th revision) appeared as either the underlying or contributory cause of death, or as an "other significant condition," were included in the study.

For each case, two individually matched controls were selected from the lists of hourly paid rubber workers. Both controls were matched to the cases by company, sex, race, and year of birth (±2 years); one of the controls was also matched to the case by year of hire (±2 years) and total duration of employment in the industry (±2 years). The selection of controls not matched by date of hire and work duration allowed for testing the hypothesis that age or calendar year, or both, of initial exposure to the rubber industry influenced the risk of bladder cancer.

WORK HISTORY

The lifetime work histories of the study subjects were abstracted from records made available by the five rubber companies and by one local union. Owing to the diversity of production job types and to the paucity of industrial hygiene data regarding chemical exposures, a system of occupational title (OT) classification was used to categorise the several hundred jobs into roughly 100 groupings (OTs) that are homogeneous with respect to materials handled and machinery used. This job classification scheme has been described in detail.[10] The 100 OTs were then aggregated into 21 mutually exclusive OT groups (OTGs). The criterion for OTG aggregation, similarity of materials and machinery used, was the same as that used to create the OTs. The smaller number of OTGs facilitated statistical analysis. Table 2 describes the 21 OTGs.

STATISTICAL ANALYSES

The work histories of the cases and controls were compared to estimate the relative risks for bladder cancer associated with work experience in each OTG. The relative risk, which is the ratio of the rate of disease among exposed people to the rate among non-exposed people, can be approximated in case-control studies by the odds ratio.[11 12] Odds ratios and χ^2 tests of association were calculated according to the methods described by Mantel and Haenszel[13] for matched samples. Years and ages of initial hire for both cases and controls were compared by means of Student's *t*-tests for paired samples. Dose-response relationships between disease risk and work experience were examined using χ^2 tests for linear trends.[14]

Table 3 *Numbers of bladder cancer cases by company and by identification source*

Company	*Source*		*Total*
	Hospital listings	*Death certificates*	
A	8	0	8
B	33	53	86
C	42	44	86
D	22	13	35
E	2	3	5
Total	107	113	220

Results

A total of 232 cases (220 men, 12 women) of bladder cancer was identified from the aforementioned sources. Because of the few women, the data analysis was restricted to the male cases and their controls. Eight male patients were black, the remainder white. Death certificates were the source of 113 of the cases; the remaining 107 were ascertained from the hospital listings. A reliable histological classification was available only for the cases identified from hospital records. Of these 107 cases, 88 (82%) had transitional cell carcinoma; other histological types included squamous cell (4), adenocarcinoma (1), allantoid papilloma (7), and undifferential carcinoma not otherwise specified (7). Table 3 shows the distribution of male cases by company and by source of identification. The median age at death for the cases identified from death certificates was 69·1 years (range 43-83) and the median age at diagnosis for the hospital-identified cases was 63·4 years (range 36-91).

Table 4 *Case-control comparisons of age and year of hire, and duration of employment for controls not matched on those factors*

	Cases (n = 20)		*Controls (n = 20)*		*Paired t-test (p)*	
	Mean	*(SEM)*	*Mean*	*(SEM)*		
Age of hire	30·1	(0·61)	30·1	(0·67)	0·05	(>0·9)
Year of hire	1927·9	(0·74)	1927·9	(0·74)	0·01	(>0·9)
Duration of employment (months)	298·1	(9·48)	285·7	(9·49)	1·13	(>0·2)

SEM = Standard error of mean.

YEAR AND AGE AT INITIAL HIRE AND DURATION OF EMPLOYMENT

Comparisons between cases and their controls not matched by age and calendar year of first employment and duration of employment are shown in table 4. As groups, the cases and controls both started work in the rubber industry at around age 30. The mean years of initial hire for both groups were also virtually identical. The cases worked longer than the controls by about 13 months. Paired *t*-tests indicated no statistically significant differences for these variables; consequently these controls were pooled with the controls matched on age and year of hire and duration of employment in the subsequent work history analyses.

ODDS RATIOS BY JOB TYPE (OTG)

Odds ratios for each of the 21 OTGs, for exposure defined as cumulative lifetime work for periods greater than one month—that is, ever v never—are presented in table 5. Of the 21 OTGs only milling (OR = 1·91) and calender operation (OR = 2·21) exhibited relative risk estimates substantially greater than the expected value of 1·00. Both were statistically significant ($p < 0·05$). Work experience in the OTG, final inspection-tyres (OR = 1·49) bore a positive, yet weaker association with bladder cancer risk.

Table 5 *Relative risk estimates for 21 occupational title groups (exposure > 1 month)*

OTG	*No exposed cases*	*No exposed controls*	*OR**	χ^2 ††
1 Batch preparation	36	69	1·07	0·07
2 Milling	26	32	1·91	4·55‡
3 Calender operation	18	19	2·21	4·51‡
4 Plystock handling	50	94	1·09	0·50
5 Extrusion	26	53	0·98	0·01
6 Fabrication-tyres, beads	60	120	1·00	0·00
7 Tubes	39	67	1·20	0·71
8 Curing preparation	23	35	1·39	1·19
9 Curing	49	102	0·95	0·07
10 Final inspection-tyres	50	77	1·49	3·01
11 Maintenance	44	87	1·02	0·01
12 General service	76	145	1·09	0·19
13 Shipping and receiving	35	55	1·31	1·39
14 Reclaim	20	36	1·13	0·16
15 Chemicals	15	26	1·17	0·22
16 Plastics	13	24	1·10	0·06
17 Preparation non-tube & tyre	40	78	1·04	0·02
18 Final inspection-tubes	13	33	0·78	0·56
19 Metal products	24	41	1·21	0·46
20 Special products	29	47	1·33	1·06
21 Unknown	23	55	0·80	0·66

*Mantel-Haenszel odds ratio for matched analysis.
†χ^2 statistic with one degree of freedom.
‡$p < 0·05$.

Relative risk estimates for these three OTGs by duration of exposure are shown in table 6. In these analyses the matching was abandoned to accommodate comparisons at multiple exposure levels. There is an apparent increase of relative risk with increasing duration of exposure to the milling and calender operation jobs; no such association was observed for final inspection-tyres.

For all three of these OTGs most exposed cases and controls worked either for short speriods (under 60 months) or for long (120 months or more). This suggests the existence of two types of worker—those with fairly high job mobility patterns and others who remain at the same jobs for extended periods.

Ever-never comparison odds ratios for the milling, calender operation, and final inspection-tyres OTGs are presented by company in table 7. Only data for companies B, C, and D are shown because of the small numbers of cases in the other two. The odds ratios for all three OTGs are raised in company C, where the greatest numbers of subjects were exposed. Odds ratios of 1·71 for final inspection-tyres for company B and 11·50 for calender operation in company D were observed, but these estimates are based on small numbers of exposed cases and controls.

Analyses by duration of exposure for these OTGs for company C are given in table 8. As was true for the total data set for all companies combined, the data for milling and calender operation suggest an increasing risk with increasing duration of exposure, although tests for linear trend were not statistically significant. There is no apparent duration-risk effect for final inspection-tyres. These findings indicate that

Table 6 *Relative risk estimates for milling, calender operation, and inspection-tyres by duration of exposure, all companies*

	Milling				*Calender operation*				*Final inspection-tyres*			
	Exposure (months)				*Exposure (months)*				*Exposure (months)*			
	<1	*1-59*	*60-119*	*≥120*	*<1*	*1-59*	*60-119*	*≥120*	*<1*	*1-59*	*60-119*	*≥120*
Cases	194	13	2	11	202	12	1	5	170	28	7	15
Controls	408	21	3	8	421	15	1	3	363	40	12	25
OR*	1·0	1·30	1·40	2·89	1·0	1·67	2·09	3·47	1·0	1·49	1·25	1·29
χ^2† for linear trend	5·76 ($p < 0·025$)				5·00 ($p < 0·025$)				1·44 ($p > 0·10$)			

*Odds ratios calculated with ≤1 month's exposure as reference group.
†χ^2 test for linear trend with 1 df.

Table 7 *Relative risk estimates for milling, calender operation, and final inspection-tyres jobs, by company*

Exposure (>1 month)	*Milling*			*Calender operation*			*Final inspection-tyres*		
	No exposed cases	*No exposed controls*	*OR**	*No exposed cases*	*No exposed controls*	*OR**	*No exposed cases*	*No exposed controls*	*OR**
Company B	3	7	0·83	1	4	0·50	6	7	1·71
Company C	12	15	2·13	9	12	1·67	37	56	1·61
Company D	4	7	1·14	5	1	11·50	4	7	1·14

*Mantel-Haenszel odds ratio for matched analysis.

Table 8 *Relative risk estimates for milling, calender operation, and final inspection-tyres by duration of exposure, company C*

	Milling			*Calender operation*			*Final inspection-tyres*		
	Exposure (months)			*Exposure (months)*			*Exposure (months)*		
	<1	*1-59*	*⩾60*	*<1*	*1-59*	*⩾60*	*<1*	*1-59*	*⩾60*
Cases	64	6	6	77	5	4	49	23	14
Controls	157	11	4	160	9	3	116	32	24
OR*	1·0	1·16	3·18	1·0	1·16	2·77	1·0	1·70	1·38
x^2† for linear trend	2·80 ($0·05 < p < 0·10$)			1·55 ($p > 0·10$)			1·72 ($p > 0·10$)		

*Odds ratio calculated with <1 month's exposure as reference group.
†x^2 test for linear trend with 1 df.

Table 9 *Mean ages and calendar years of initial exposure to three OTGs among ever-exposed subjects in company C*

	No	*Age*	*Calendar year*
Milling			
Cases	12	40·5 (3·37)*	1933·4 (3·49)
Controls	15	35·5 (3·18)	1936·5 (3·48)
Calender operation			
Cases	9	39·7 (4·69)	1935·9 (5·68)
Controls	12	39·2 (4·55)	1936·4 (4·10)
Final inspection-tyres			
Cases	37	32·9 (1·92)	1928·2 (2·54)
Controls	56	33·0 (1·52)	1928·2 (1·86)

*Standard error of mean.

for milling and calendering, the OTGs for which the most consistent results obtained, any excess bladder cancer risks may be ascribed to exposures in company C.

Table 9 shows comparisons of mean age and calendar year of initial exposure for cases and controls in company C who had ever worked at milling, calender operation, or final inspection-tyres. The similarities of these values for cases and controls indicate no apparent association between age or secular period of first exposure and excess risk of bladder cancer. Virtually identical results were obtained for ever-exposed cases in all companies combined.

Discussion

Previous studies in the British rubber industry[1 2 15] have shown that rubber workers exposed to antioxidants and accelerators used in tyre manufacturing have experienced excess bladder cancer morbidity and mortality. The specific agents identified most convincingly as bladder carcinogens are beta-naphthylamine, 4-aminobiphenyl, and 4-4′-diaminobiphenyl (benzidine).[1 16]

The present study was an attempt to identify high risk work areas defined by job type. The lack of past environmental data precluded analysis according to chemical exposures, per se; consequently, the occupational title grouping was used as an exposure surrogate. This study can therefore be viewed as exploratory in nature, primarily because we had no objective information and uncertain expectations regarding the locations and intensities of exposures to bladder carcinogens. A case-control study design was the method of choice because it permitted evaluation of workers' entire job histories, a necessary advantage in view of the extensive job mobility patterns in the rubber industry.

An increased risk of bladder cancer was observed for milling and calender operation jobs, and to a lesser extent for final inspection of tyres. The relative risk estimates for milling and calender operation were not excessive (about 2·0), but there

were positive trends with increasing duration of exposure. The risks for all three OTGs were apparently localised to one company (company C).

Milling and calender operation are both early processes in tyre production and both entail handling of heated uncured stock; there is some potential for exposure to volatilised rubber chemicals including antioxidants, antiozidants, accelerators, and organic solvents.[17 18] Environmental exposure in final inspection-tyres is primarily to particulates resulting from the buffing and grinding of the cured products.[17]

Several rubber chemicals may possibly generate aromatic amines. Chief among these are N-nitrosodiphenylamine, diphenylamine, aldol-alpha-naphthylamine, phenyl-alpha- and phenyl-beta-naphthylamine (PBNA). The carcinogens beta-naphthylamine (BNA), 4-aminobiphenyl, and 4,4′-diaminobiphenyl have not been used to any appreciable extent in the rubber industry. Instead, PBNA has been the antioxidant of choice during the years of relevant exposures in this study. PBNA may be partially metabolised to BNA in man,[19] and it is also possible that exposure to BNA may have resulted from BNA impurities in PBNA. Had exposure to BNA been significant then it would have been expected that workers in the batch preparation areas would have experienced an excess risk of bladder cancer. This was not the case in this study, nor in the investigation reported by Monson and Fine.[20]

The current finding that two job types, milling and calender operation, were associated with a historical hazard from bladder cancer needs to be viewed with caution for several reasons. As mentioned previously, job types were used as surrogate measures of exposure in lieu of quantified industrial hygiene data. Moreover, the complexity of the chemical environment in the rubber industry and the extent of job mobility preclude direct risk assessment for occupational groups exposed to clearly defined, circumscribed exposures. A second consideration is that we had no data on potential confounding factors, such as cigarette smoking,[21 22] coffee consumption,[23] and on less easily measured variables such as abnormal tryptophan metabolism[24] and detoxifying acetylating enzyme activity.[25] It was assumed that these factors would not be distributed idiosyncratically by job so as to distort the findings, but this assumption lacks verification.

Establishment of the aetiological association of job type and the risk of bladder cancer will require a better characterisation of the work environments in the milling and calender operation areas with regard to chemical exposures. In particular, historical reconstruction of chemical use and current identification of the sources and levels of aromatic amines and other potential carcinogens will be critical. Studies of other, similarly exposed populations should also be informative.

We thank the five rubber and tyre companies and the United Rubber Workers Union for their support and co-operation. We also thank Dr A C Guira for allowing us access to his data, Mr Robert Holbrook and Mr Timothy Harrell for data collection, and Ms Jackie Brown and Ms Anita Warren for manuscript preparation. This research was supported in part by a grant from the National Cancer Institute through the National Bladder Cancer Project, Control No 1-R26-CA15950.

References

[1] Case RAM, Hosker ME. Tumour 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.
[2] Veys CA. Two epidemiological inquiries into the incidence of bladder tumors in industrial workers. *J Natl Cancer Inst* 1969;**48**:219-26.
[3] Cole P, Hoover R, Friedell GH. Occupation and cancer of the lower urinary tract. *Cancer* 1972;**29**:1250-60.
[4] Mancuso TF, El-Attar AA. Cohort study of workers exposed to beta-naphthylamine and benzidine. *J Occup Med* 1967;**9**:277-85.
[5] Fox AJ, Collier PF. A survey of occupational cancer in the rubber and cablemaking industries: analysis of deaths occurring in 1972-4. *Br J Ind Med* 1976;**33**:249-64.
[6] Monson RR, Nakano KK. Mortality among rubber workers. I White male union employees in Akron, Ohio. *Am J Epidemiol* 1976;**103**:284-96.
[7] Monson RR, Nakano KK. Mortality among rubber workers. II Other employees. *Am J Epidemiol* 1976;**103**: 297-303.
[8] McMichael AJ, Andjelkovich DA, Tyroler HA. Cancer mortality among rubber workers. *Ann N Y Acad Sci* 1976; **271**:125-37.
[9] Guira AC. Bladder carcinoma in rubber workers. *J Urol* 1971;**106**:548-52.
[10] Gamble JF, Spirtas R. Job classification and utilization of complete work histories in occupational epidemiology. *J Occup Med* 1976;**18**:399-404.
[11] Cornfield J. A method of estimating comparative rates from clinical data. Applications to cancer of the lung, breast and cervix. *J Natl Cancer Inst* 1951;**11**:1269-75.
[12] Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976;**103**:226-35.
[13] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;**22**:719-48.
[14] Armitage P. Tests for linear trends in proportions and frequencies. *Biometrics* 1955;**11**:375-86.
[15] Davies JM. Bladder tumours in the electric-cable industry. *Lancet* 1965;ii:143-6.
[16] Hueper WC. *Occupational and environmental cancers of the urinary system.* New Haven: Yale University Press, 1969: 229-54.
[17] Williams TM, Harris RL, Arp EW, Symons MJ, Van Ert MD. Worker exposures to chemical agents in the manufacture of rubber tires and tubes: particulates. *Am Ind Hyg Assoc J* 1980;**41**:204-11.
[18] Van Ert MD, Arp EW, Harris RL, Symons MJ, Williams TM. Worker exposures to chemical agents in the

manufacture of rubber tires: solvent vapor studies. *Am Ind Hyg Assoc J* 1980;**41**:212-9.

[19] Finklea JF. Current NIOSH intelligence bulletin: metabolic precursors of a known human carcinogen, beta-naphthylamine. *Am Ind Hyg Assoc J* 1977;**38**:A21-3.

[20] Monson RR, Fine LJ. Cancer mortality and morbidity among rubber workers. *J Natl Cancer Inst* 1978;**61**: 1047-53.

[21] Lilienfeld AM, Levine ML, Moore GE. The association of smoking with cancer of the urinary bladder in humans. *Arch Intern Med* 1956;**98**:129-35.

[22] Cole P, Monson RR, Haring H, Friedell GH. Smoking and cancer of the lower urinary tract. *N Engl J Med* 1971; **284**:129-34.

[23] Cole P. Coffee-drinking and cancer of the lower urinary tract. *Lancet* 1971;i:1335-7.

[24] Bryan GT. The role of urinary tryptophan metabolites in the etiology of bladder cancer. *Am J Clin Nutr* 1971;**24**: 841-7.

[25] Lower GM Jr, Nilsson T, Nelson CE, Wolf H, Gamsky TE, Bryan GT. N-acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. *Environ Health Persp* 1979;**29**:71-9.