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# The Copenhagen case-referent study on bladder cancer

## Risks among drivers, painters and certain other occupations[1]

by Ole M Jensen, MD, DrMedSc,[2] Jürgen Wahrendorf, DrScMathHabil,[3] Jens B Knudsen, MD,[4] Bent L Sørensen, MD, DrMedSc[4]

JENSEN OM, WAHRENDORF J, KNUDSEN JB, SØRENSEN BL. The Copenhagen case-referent study on bladder cancer: Risks among drivers, painters and certain other occupations. *Scand J Work Environ Health* 13 (1987) 129—134. Occupational risk of bladder cancer (including papilloma) was investigated as part of a case-referent study in Copenhagen. Occupational histories were obtained on 389 cases and 790 referents drawn at random from the general population of the study area. When persons with missing information were excluded, a total of 371 cases (280 men, 91 women) and 771 referents (577 men, 194 women) were left for analysis. After adjustment for tobacco smoking, age, and sex, significantly increased relative risks were observed for occupation in land transport, in particular bus, taxi, or truck driving. A statistically significant trend was seen with duration of employment in these trades. Based on a logistic regression analysis, a relative risk (RR) of 1.3 was determined for 10 years of employment in the trade. An association was also found for employment in trades undertaking painting (RR = 1.4 for 10 years' employment), and a significant trend emerged for duration of employment. A positive association with employment in the textile and leather industry disappeared after adjustment for tobacco smoking, and no association with duration of employment emerged. No association was found with employment in the chemical, rubber, iron and metal industries or in health services.

*Key terms:* chemical, driving, health services, iron and metal, painting, rubber, trucking.

The incidence of bladder cancer in Denmark is among the highest in those parts of the world where papillomas of the urinary bladder are included with the frankly invasive tumors in cancer incidence statistics (22). Within Denmark the incidence is particularly high in Copenhagen (8), where tobacco smoking has been identified as the most important risk factor in the past (17), and also in the present study (15). This study was conducted to shed light on additional exogenous factors, which may be associated with the high bladder cancer incidence in Copenhagen in particular.

Among such factors, occupational exposures are known to increase the risk of bladder cancer. 2-Naphthylamine, benzidine, auramine, and magenta produced from aniline, as well as 4-aminobiphenyl are recognized bladder carcinogens (13). Increased risks have been recorded among persons in industries using aromatic amines, such as among rubber workers in Great Britain and among dyers in the textile industry. Increased risks have also been reported among hair dyers, machinists, and truck drivers (4, 7, 18, 21, 23).

In Denmark, Lockwood's case-referent study, published in 1961 (17), is suggestive of an increased risk for workers in the skin, leather, rubber, iron and metal industries, in construction, and in work on railways and tramways. The appropriateness of the comparison between cases and a national survey is, however, doubtful, as pointed out by the author, but similar associations have also been found in the United States (7). Exposure to gasoline and oil products has been suggested to be of etiological importance in Denmark (19), and an analysis of a linked data set from the Cancer Registry and the Danish Supplementary Pension Fund indicates a significantly increased risk among men ever employed in printing, the manufacture of paint and glue products, the manufacture of electricity and gas, and among persons working in pharmacies and paint shops (20). The present paper reports on risks associated with previous employment in certain occupations, as recorded in a case-referent study conducted in Copenhagen between 1978 and 1981.

## Subjects and methods

### *Cases*

The investigation includes tumors located in the urinary bladder only. As the clinical distinction between noninvasive (papilloma) and invasive tumors

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of the urinary bladder is difficult (5), the two have been grouped together under the term "bladder cancer."

Ascertainment of the cases and referents for the study and the interviewing techniques have been described in detail elsewhere (14); to be eligible for study the persons representing the cases and the referents had to be alive. From May 1979 to April 1981 a total of 412 patients living in the municipalities of Copenhagen and Frederiksberg and the county of Copenhagen were reported to the study, and 389 of these, or 94.4 %, were interviewed. A comparison with the records of the Cancer Registry for the population and time period in question shows the case group to be a representative sample of all bladder cancer cases arising in Greater Copenhagen with regard to age, sex, place of residence by area, and broad occupational groups. For some 99 % of the men and all of the women the bladder tumors were histologically verified; 89.4 % of all the tumors were of the transitional cell type, of which 66.6 % were Bergquist grade 0 to 2 (2). Altogether 61.2 % of the tumors were in stages Ta without infiltration or T1 with infiltration of subepithelial connective tissue only; 3.6 % were T4 tumors, ie, with fixation. The majority of cases was thus investigated in early stages of disease development.

*Referents*

The referents were selected at random in April 1979 among the residents of the municipalities where the cases were living, covering a total population (below the age of 75 years) of 552 071 men and 577 382 women on 1 January 1980. The sample was stratified to group-match the cases with regard to sex and age in five-year age groups. As all the referents were drawn at the beginning of the study, some had died or moved out of the area when approached for interview during the following two years. Such persons were replaced with new persons drawn at random from the list of residents in the same age and sex groups. Among the 1 052 referents approached, the overall participation rate was 75.1 %.

*Interviews*

Interviews were usually conducted in the persons' home by a trained interviewer, who was not informed of the interviewee's status as a case or referent. A structured questionnaire was used to obtain information on known or suspected risk factors for bladder cancer. The questions concerned tobacco smoking, drinking of coffee, tea and other beverages, use of artificial sweeteners, use of drugs, other medical procedures, previous medical conditions, and occupation.

Questions were asked about specific occupational exposures, and an occupational history was then constructed for each person, from systematic requests for information about single employments (company, industry, type of work performed, place of work, periods of employment). The information was coded according to industry by means of an extended Danish version of the International Standard Industrial Classification (ISIC) of all economic activities (10). Jobs were classified according to the Danish occupational classification code used for the 1970 census (9).

*Statistical analysis*

After initial scrutiny of the specific occupations, the occupational histories of the cases and referents were summarized as the total duration of employment in certain occupations. This procedure permited both simple analyses comparing persons ever with those never employed in a given industry and investigations of the association of bladder cancer with the duration of employment in a given industry.

The statistical analysis was carried out by unconditional maximum likelihood estimation of the parameters of a logistic regression model (3) using the generalized linear interactive modelling (GLIM) package (1). As cigarette smoking was found to be the most important determinant of bladder cancer, it was fully controlled by including the following three smoking-related variables: two dichotomous variables qualifying whether a person (a) had ever smoked and (b) was currently smoking and a continuous variable quantifying the lifetime cigarette exposure by the logarithms of pack-years, as described elsewhere (15). All the models investigated accounted also for age and sex. The confidence limits were based on the asymptotic theory of maximum likelihood estimates.

Scrutiny of the data did not lead to the identification of other potentially confounding variables. Individuals for whom single pieces of information were missing were excluded from the analysis, the result leaving 371 cases (280 men, 91 women) and 771 referents (577 men, 194 women). For the logistic regression analysis the maximum number of individuals with complete information on the variables of interest was used.

## Results

Table 1 shows the number of cases and referents ever and never employed in a given industry, as well as the estimated relative risks (RR) adjusted for age and sex. Significant increased relative risks were observed for employment in the textile and leather industry (ISIC 32), in painting [ISIC 50150 (painting firms), 39097 (sign post factories and sign post painters), 95133 (automobile painters), 33209 (furniture lacquering and painting), 38196 (industrial painting)], and in land transport (ISIC 711). Table 2 gives the results of the logistic regression analysis when duration of employment in land transport, driving, painting, and the textile and leather industries, respectively, were regarded as continuous variables, adjusted for age, sex, and the three smoking variables. As effect measures the relative risk estimates associated with 10 years of

**Table 1.** Relative risk of bladder cancer in Copenhagen in 1979—1981 for certain industries.

| Industry | ISIC[a] | Cases | | Referents | | Relative risk[b] | 95 % confidence intervals |
|---|---|---|---|---|---|---|---|
| | | Ever | Never | Ever | Never | | |
| Textile and leather | 32xxx | 56 | 315 | 78 | 693 | 1.66 | 1.14—2.43 |
| Chemical | 35xxx | 31 | 340 | 52 | 719 | 1.26 | 0.79—2.00 |
| Rubber | 355xx | 2 | 369 | 4 | 767 | 0.98 | 0.18—5.38 |
| Iron and metal | 38xxx | 85 | 286 | 199 | 572 | 0.85 | 0.64—1.25 |
| Painting | c | 13 | 358 | 11 | 760 | 2.54 | 1.12—5.73 |
| Land transport | 711xx | 51 | 320 | 73 | 698 | 1.55 | 1.06—2.28 |
| Health | 933xx | 23 | 348 | 42 | 729 | 1.18 | 0.69—2.01 |

[a] Danish version (10) of the International Standard Industrial Classification.
[b] Adjusted for sex and age in the logistic regression model.
[c] Codes 33209 = furniture lacquering and painting, 38196 = industrial painting, 39097 = sign post factories and sign post painters, 50150 = painting firms, and 95133 = automobile painting.

**Table 2.** Logistic regression estimates of the parameters for duration of employment in certain industries[a] in the Copenhagen case-referent study of bladder cancer, 1979—1981.

| Model number | Variable considered | Deviance | Degrees of freedom | Relative risk[b] | 95 % confidence interval |
|---|---|---|---|---|---|
| 1 | Base-line model adjusted for sex, age and smoking[c] | 1 382 | 1 132 | . | . |
| 2 | Duration of land transport occupation | 1 377 | 1 131 | 1.28 | 1.04—1.45 |
| 3 | Duration of occupation as bus, taxi or truck driver | 1 376 | 1 131 | 1.29 | 1.05—1.59 |
| 4 | Duration of occupation as painter | 1 377 | 1 131 | 1.39 | 1.04—1.86 |
| 5 | Duration of occupation in textile and leather industry | 1 380 | 1 131 | 1.13 | 0.94—1.36 |
| 6 | Duration of occupation as printer (4) or driver (3) | 1 371 | 1 130 | 1.41<br>1.30 | 1.05—1.89<br>1.06—1.61 |

[a] For the ISIC codes of occupation see table 1.
[b] Associated with 10 years of occupation.
[c] Three smoking variables: ever smoked, stopped smoking and logarithm of pack-years. (For details see reference 14.)

employment have been derived as exp (10 b), where b is the estimated regression coefficient. The reduction of deviance, as well as that of the confidence intervals, showed a significant association (5 % level) between bladder cancer and employment in land transport (RR = 1.28), bus, taxi or truck driving (RR = 1.29), and painting (RR = 1.39). By contrast, duration of employment in the textile and leather industry was not a significant risk determinant in this smoking adjusted analysis. In addition, there was no clear trend in the relative risk with duration of employment in this industry when examined in a categorical fashion by 10-year intervals.

Model 6 in table 2 shows that there was little potential for two single occupations to confound each other, as there was no substantial change in the coefficients when occupation as a painter (model 4) and occupation as a bus, taxi or truck driver (model 3) were included jointly in the regression model.

The association between bladder cancer and employment in land transport trades comprising railroads (ISIC 71110), bus services (ISIC 7112), taxi services (ISIC 7113), trucking (ISIC 7114), and other transport services (ISIC 7115) is shown in further detail in table 3. There was a significant trend of increasing relative risks of bladder cancer with increasing duration of employment in land transport in general, and, when restricted to bus, taxi and truck services, ie, excluding employment on railroads (ISIC 7111X) and other transport services (ISIC 7115X).

Regression coefficients and relative risks were also estimated for the employment of 24 cases and 57 referents in sea transport (ISIC 712) (RR 0.9, 95 % confidence interval (95 % CI) 0.5—1.4) and for the subgroup (2 cases, 9 referents) of machinists and stokers at sea (ISIC 712, partly) (RR 0.4, 95 % CI 0.1—1.7). Neither of these risk estimates were thus significantly different from 1.

There were 13 cases and 11 referents who had been employed in painting trades, and, among these, five cases and seven referents had a duration of employment between one and nine years, while the remaining eight cases and four referents were employed for 20 years or more. Table 4 shows the clearly increased relative risks as well as the significant positive trend (P = 0.017, two-sided).

**Table 3.** Relative risk estimates and the test for trend of bladder cancer in Copenhagen in 1979—1981 in association with duration of employment in land transport.

| Duration of employment (years) | Land transport | | | | Bus, taxi and truck drivers | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases (N) | Referents (N) | Relative risk[a] | 95 % confidence interval | Cases (N) | Referents (N) | Relative risk[a] | 95 % confidence interval |
| 0 | 320 | 698 | 1.0 | · | 329 | 713 | 1.0 | · |
| 1—9 | 12 | 33 | 0.8 | 0.4—1.5 | 11 | 31 | 0.7 | 0.4—1.5 |
| 10—19 | 15 | 17 | 1.7 | 0.8—3.5 | 13 | 15 | 1.6 | 0.8—3.4 |
| 20—29 | 12 | 6 | 3.7 | 1.3—10.1 | 9 | 4 | 3.5 | 1.1—11.6 |
| ≥ 30 | 12 | 17 | 1.7 | 0.8—3.8 | 9 | 8 | 2.4 | 0.9—6.6 |
| Z-value for trend | · | · | 2.56 | P = 0.01[b] | · | · | 2.60 | P = 0.009[b] |

[a] Adjusted for age, sex, and three smoking variables in the logistic regression model.
[b] Two-sided test for trend.

**Table 4.** Relative risk (RR) estimates and the test for trend for different durations of employment as a painter[a] — Copenhagen, 1979—1981. (95 % CI = 95 % confidence interval)

| Duration of employment (years) | Cases (N) | Referents (N) | RR[b] | 95 % CI |
|---|---|---|---|---|
| 0 | 358 | 760 | 1.0 | · |
| 1—19 | 5 | 7 | 1.6 | 0.5—5.5 |
| ≥ 20 | 8 | 4 | 4.1 | 1.2—13.9 |
| Z-value for trend | · | · | 2.38 | P = 0.017[c] |

[a] See table 1.
[b] Adjusted for age, sex, and three smoking variables in the logistic regression.
[c] Two-sided test for trend.

## Discussion

The present study indicates that the risk of bladder cancer in Copenhagen is increased among persons who have been employed in the land transport services or as a painter. By contrast, no increased risk was found for persons in the chemical industry, the iron and metal industry, and the rubber industry or among health personnel (table 1). The indication of an increased risk for employment in the textile and leather industry did not persist when smoking was accounted for, and there was no association with duration of employment.

For all occupations associated with bladder cancer risk in the present study, estimates of risk associated with 10 years of occupation, as well as their confidence intervals (table 2) were almost identical with the estimates and confidence intervals determined for males and smokers. In other words, the effect of occupation was basically found for male smokers, for whom it however represents a significant increase over the smoking-related risks for which the model was adjusted.

The increased relative risks among persons employed in land transport services persisted after thorough adjustment for smoking (tables 2 and 3). The risk was primarily confined to bus, trucking, and taxi services with a two- to threefold increase for persons employed for 10 or more years. The association could not have been biased by interviewer or interviewee suspicion of such an association from other studies, as the data collection and coding were performed prior to reports emerging from North America. The association was very specific, as no increased risks were observed among persons working in the railway services, in other transport services (eg, car rental) or in transport services at sea. The increasing risk with duration of employment points to a biologically meaningful association.

The present findings corroborate results of recent reports of an increased risk of bladder cancer among truck drivers in the United States. The bladder cancer risk has been associated with exposure to diesel fumes (12, 21). An increased risk with such exposure also emerged from a British mortality study of bladder cancer (6). It has however been pointed out that exposure to diesel fumes is unlikely to be the sole explanation, since the risks have also been determined for nondiesel exposed drivers (11), and exposure to traffic exhaust has been offered as another possible explanation (11). Most trucks and buses, as well as a large proportion of taxis in Denmark, have diesel engines, but no information on diesel exhaust exposure was collected in the present investigation. The increased risk associated with employment in land transport services in Copenhagen might be explained in this way. As another possibility, persons in the transport services may have an increased exposure to gasoline and grease, which have been suggested to increase the risk of bladder cancer in Denmark (19).

In another paper from this study (16), we reported on the results in relation to beverage consumption. Total liquid consumption was found to be related to bladder cancer risk, and it was speculated that this finding might be related to the regularity of bladder emptying, which had also been brought up as a possible explanation of increased bladder cancer risk among truck drivers (11). Therefore, in the present analysis we investigated the possibility that total liquid

consumption and duration of employment as a driver might be confounding each other, but we did not find any such effect.

A fourfold increased risk was noted among persons with long-term employment in the application of paint in various trades (table 4). In a study of the total Danish Cancer Registry material for the years 1970—1979 (20) an increased risk of lower urinary tract cancer (ie, bladder, renal pelvis, ureter, and urethra) was found among persons in paint and glue manufacturing, and among those with a work history in paint shops and pharmacies. An increased risk of bladder cancer among painters has previously been described in the United States (23), whereas other studies have not reported such an association. Persons in these trades are likely to be in contact with a large variety of chemical and complex mixtures, and the nature and composition of these mixtures may vary from one country to the other and thus influence the consistency of the observation.

In conclusion, the present study shows an increased risk of bladder cancer among persons who have been employed in the transport services, including buses, trucks and taxis, in Copenhagen. The explanation for this increased risk, primarily among men, is unclear, but the reality of the finding is strengthened by an association with duration of employment and by similar results emerging from studies elsewhere. If truely causal, as much as 5 % of all bladder cancer cases in Copenhagen can be considered attributable to employment in land transport services. The examination of urinary concentrations of compounds associated with diesel fuels, traffic fume exposure in general, and gasoline or grease exposure in these trades may be rewarding, both with regard to the understanding of bladder carcinogenesis and with a view to prevention. Similar studies of biological samples and of the work environment should be pursued among painters. Confirmation of the present results by studies of cohorts with well-defined occupational exposures should also be attempted.

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