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Work-related Bladder Cancer Risks in Male Japanese Workers: Estimation of Attributable Fraction and Geographical Correlation Analysis

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One hundred and forty-nine relative risks (RRs) on occupations and bladder cancer were extracted from 27 case-control studies and geometric means were calculated for 27 occupations as summary RRs. Those in high risk occupations, among whom the summary RRs significantly exceeded unity, were found to be petroleum workers (RR=3.51), dye workers (RR=3.38), machinists (RR=2.76), drivers (RR=2.22), rubber workers (RR=2.19), printers (RR=2.12), clothing/tailors (RR=2.10), wood workers/carpenters (RR=1.70), miners (RR=1.68), textile workers (RR=1.63), mechanics (RR=1.54), engineers (RR=1.54), leather workers (RR=1.49), painters (RR=1.48) and chemical workers (RR=1.44). The estimated numbers of male bladder cancers in 1980 in the high risk and other occupations were 820 and 2065 cases, respectively. The estimated number of work-related bladder cancer was 548 cases, the attributable fraction being 19% in active employees and 12% in the entire population. The geographical distribution of male bladder cancer deaths in Japan was positively correlated with the distributions of workers in the transport/communications industry and in tertiary industries including services, wholesale, retail, finance and insurance, whereas it was negatively correlated with the distribution of workers in the agricultural industry. These findings suggest that workers in certain industries may be at high risk of bladder cancer, but lifestyle modification associated with urbanization and industrialization could be an alternative explanation.

Key words: Occupation — Bladder cancer — Epidemiology — Attributable fraction — Geographical distribution

The incidence rate of bladder cancer (ICD=188) among Japanese is lower than in other industrialized countries.[1,2] The cumulative incidence rate among males for age 0 to 74 years ranges from 0.75 per 100 per year in Miyagi Prefecture to 1.18 in Nagasaki City as compared to 3.23 in Varese, Italy, 2.95 in Connecticut, US (whites) and 1.99 in England and Wales.[3] As suggested by this fact, there must be some difference in the prevalence of risk factors between Japan and other industrialized countries, but thus far no risk factors have been found to explain the risk difference.

Occupational exposure to carcinogens is one of the established risk factors for bladder cancer.[2] Among 26 human carcinogens and industrial processes for which sufficient evidence of carcinogenicity in workers has been accumulated, sixteen (62%) are considered to increase the risk of bladder cancer.[4] When the low risk of bladder cancer in Japan is linked with the role of occupational exposures in bladder carcinogenesis, it is possible to infer that the fraction of bladder cancers attributable to occupational exposures is smaller in Japan. On the other hand, the number of occupational bladder cancers among Japanese dyestuff workers exposed to benzidine or 2-naphthylamine totals 372 as of 1984 according to workers' compensation files[5] and the list of occupations and industries which are presumably related to the risk of bladder cancer is still expanding.[6] Thus, the incidence of occupational bladder cancer may be higher than expected, being masked by a lower incidence of non-occupational cases when compared to other industrialized countries.

The object of the present study was to estimate the fraction of work-related bladder cancer incidence among male Japanese workers. The term "work-related" is used in place of the conventional term "occupational" to cover not only occupational exposures but also risk factors which are differentially distributed by occupation and industry in Japan.

MATERIALS AND METHODS

In the first part of the study, the fraction of bladder cancer incidence which can be considered as work-related is estimated from existing epidemiological data. In the second part, the geographical distribution of bladder cancer deaths in Japan is analyzed in relation to the distribution of workers in different industries in order to examine the possible role of work-related factors identified in the first part.

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Estimation of attributable fraction Original articles published in the period 1972 to 1989 were systematically reviewed to identify risk estimates for occupations and bladder cancer. Relative risk (RR) estimates for various work categories and bladder cancer were extracted from case-control studies. Cohort studies and nested case-control studies, i.e. case-control studies within cohorts of workers, were excluded. A summary relative risk was calculated from extracted RRs for each occupation as a geometric mean weighted by the numbers of bladder cancer cases in case-control studies. The 95% confidence interval (CI) was also obtained from the geometric standard error of each summary RR. Occupations for which the summary RRs were significantly higher than unity when the 95% CIs were referred to were selected as high risk occupations. Occupations for which the number of extracted RRs was less than 3 were not selected because the number of estimates was too small to calculate 95% CIs.

To estimate the number of incident cases of bladder cancer among male workers in a certain occupational category, the indirectly age-adjusted incidence rate in that occupational category, given that there is no excess risk, was first calculated, and then the incidence rate was adjusted to the summary RR of that occupational category by using the following formula (see Appendix for details):

$$I_k = \frac{RR_k \times I_p}{1 - \sum_j P_j + \sum_j P_j \times RR_j},$$

where I_k and I_p denote the incidence rates among workers in high risk occupational category k and among all workers, respectively, RR_j the summary RR and P_j the proportion of workers in occupational category j in the general population. Five-year age categories from 15 to 69 were considered as the population at risk and the numbers of workers in different occupational categories and their age distributions were obtained from the National Census of 1980.[7] The age-specific incidence rates of bladder cancer were obtained from a report by the Research Group for Population-based Cancer Registra-

Table I. Summary Relative Risks for Different Work Categories

Category	RR	95%CI	References[a]
Petroleum	3.51	2.13–5.78	10–16
Dye	3.38	2.21–5.19	10, 12, 17–20
Machinist	2.76	1.93–3.96	11, 12, 14, 16, 21–23
Driver	2.22	1.56–3.14	12, 14, 21–29
Rubber	2.19	1.38–3.46	10–14, 18, 19, 28–30
Printer	2.12	1.66–2.72	10, 13, 14, 17–19, 21–23, 31, 32
Clothing/tailor	2.10	1.37–3.23	12, 14, 16, 18–20
Wood/carpenter	1.70	1.03–2.82	14, 16, 21, 22, 33
Miner	1.68	1.35–2.11	14, 19, 23, 29
Textile	1.63	1.03–2.58	13, 14, 16, 18, 21, 28, 32
Mechanic	1.54	1.06–2.24	12, 14, 18, 21–23, 25, 32, 34
Engineer	1.54	1.01–2.34	14, 16–18, 22
Leather	1.49	1.03–2.16	10, 12, 14, 17–19, 22, 28, 35
Painter	1.48	1.06–2.08	10–12, 14, 28
Chemical	1.44	1.05–1.98	10–12, 14–16, 19–21, 23, 28, 34, 36
Photographer	3.00	—	12
Brick	2.00	—	18
Plastic	1.83	—	18, 19
Welder	1.70	—	12, 14
Diesel exhaust[b]	1.69	—	20, 25
Food processor	1.60	—	12
Plumber	1.41	—	22, 23
Motor manufacturer	1.14	0.80–1.64	14, 18, 28, 29
Hairdresser	1.01	—	14, 17
Construction	0.97	0.31–3.02	14, 21, 23
Cable	0.59	—	12, 13
Paper production	0.50	—	33

a) See the reference list.
b) Workers exposed to diesel exhaust.

tion in Japan.[8] The fraction attributable to an occupational category was calculated by using the following formula (see Appendix for details):

$$AF=\frac{\sum_j P_j \times RR_j - \sum_j P_j}{1-\sum_j P_j + \sum_j P_j \times RR_j}.$$

Geographical correlation analysis The country of Japan is divided into 47 administrative regions (46 prefectures and the Tokyo Metropolitan area). To evaluate the risk of death from bladder cancer in male residents of each region, a summary risk score was calculated for each region by summarizing two standardized mortality ratios (SMRs) of 1979–81 and 1984–86 in each region to that of the entire country[9] by principal component analysis. Each region was then classified into a low, medium or high risk area according to the summary risk score, i.e. the first principal component value, the cutoff points being 25 percentile and 75 percentile values.

The proportions of male workers in 5 major industries (agriculture, manufacturing, transport/communications, construction and service/wholesale, retail/finance, insurance) in the total population of those aged 15 to 69 were obtained for each region from the National Census[7] and compared between high, medium and low risk areas by the one-way analysis of variance (ANOVA) procedure.

RESULTS

Estimation of attributable fraction Sixty original articles on occupations and bladder cancer, 26 cohort studies and 34 case-control studies, were reviewed. Of the 34 case-control studies, 7 were excluded because they were based on specific cohorts of workers or other groups not representing general populations. From the 27 remaining case-control studies, 149 RRs were extracted for 27 occupations, including non-significant results (Table I).[10-36] Fourteen occupations for which the summary RR significantly exceeded the null value were selected as high risk occupations. The summary RR was the highest for petroleum workers (RR=3.51), followed by dye workers (RR=3.38). The occupational categories which showed intermediate magnitude of risk (2<RR<3) were machinists (RR = 2.76), drivers (RR = 2.22), rubber workers (RR=2.19), printers (RR=2.12) and clothing/tailors (RR=2.10). The excess in risk was marginal (RR<2) in wood workers/carpenters (RR=1.70), miners (RR=1.68), textile workers (RR=1.63), mechanics (RR=1.54), engineers (RR=1.54), leather workers (RR=1.49), painters (RR=1.48) and chemical workers (RR=1.44). Of the remaining 13 occupations, 11 were not selected because the number of RRs was too small

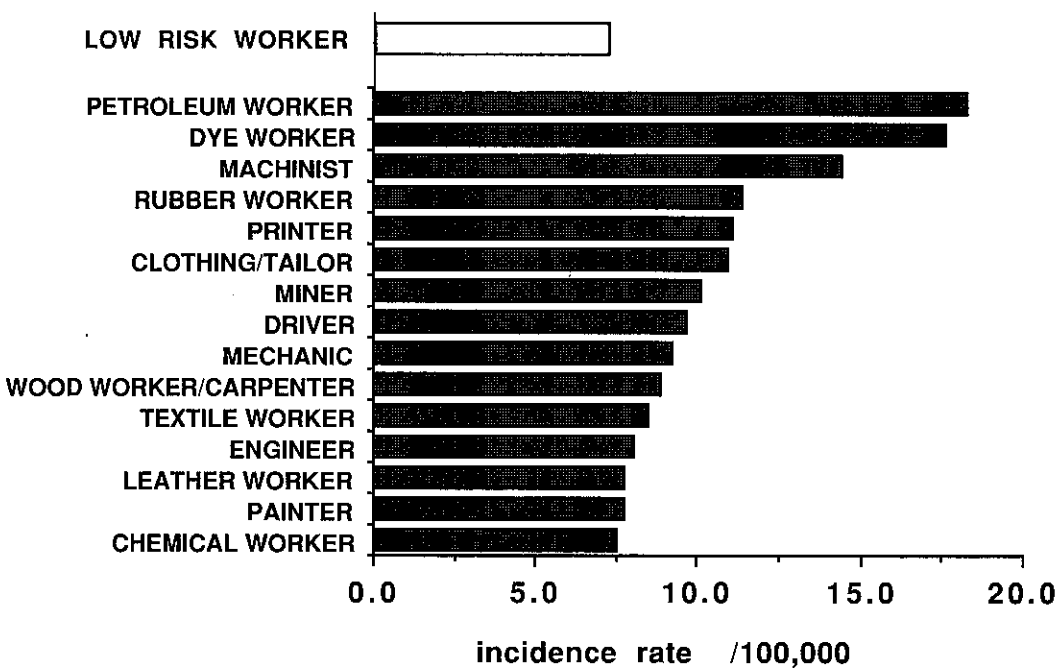

Fig. 1. The estimated incidence rates of bladder cancer among male Japanese workers in high risk occupations in 1980.

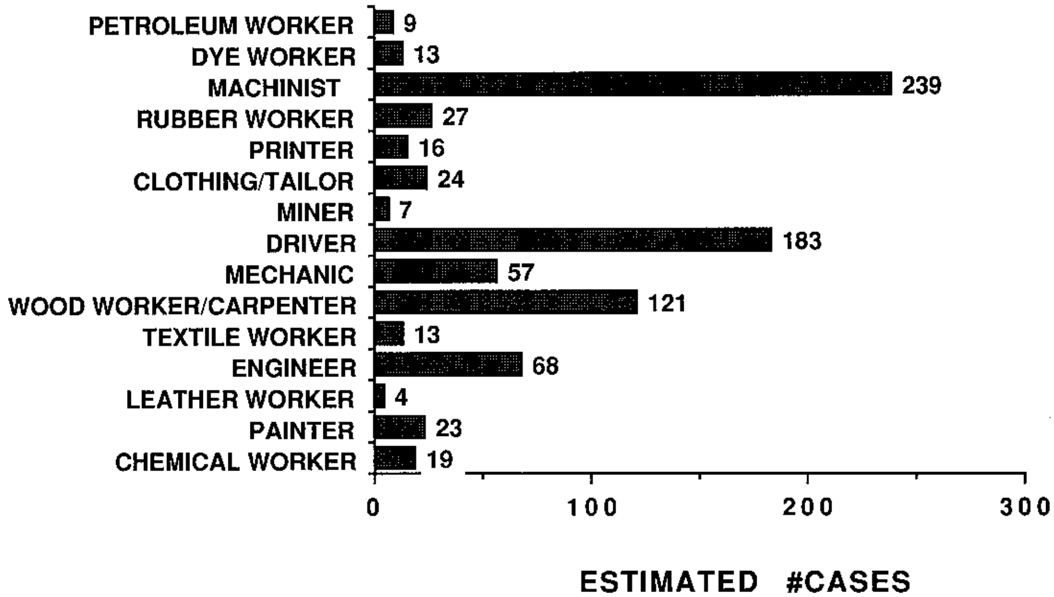

Fig. 2. The estimated numbers of bladder cancer newly diagnosed in 1980 among male workers in high risk occupations.

Table II. Estimated Numbers of Bladder Cancer Cases in 1980 among Japanese Males Aged 15 to 69 in Different Working Situations

Working situations	Population	Incidence rate per 100,000	Number of cases
All employed	35,679,000	8.1	2,885
high risk occupation	7,907,000	10.4	820
low risk occupation	27,772,000	7.4	2,065
Unemployed	10,175,000	17.3	1,758
Total population	45,854,000	10.1	4,643

and two occupations because the summary RRs did not significantly exceed unity.

The estimated incidence rates of bladder cancer in different occupational groups are shown in Fig. 1. The annual incidence rate among low risk workers was also estimated to be 7.4 per 100,000. The numbers of bladder cancer cases diagnosed in 1980 were determined by applying the estimated incidence rates to the numbers of workers, as shown in Fig. 2. The total number of bladder cancer diagnosed in 1980 was estimated to be 4,643 cases among Japanese males and 2,885 cases among active workers aged 15 to 69. Of the latter, 820 cases were estimated to have occurred among the high risk workers, the corresponding incidence rate being 10.4 per 100,000, as shown in Table II. The fraction attributable to work-related risks was estimated to be 19% among active workers and 12% in the entire male population.

Geographical correlation analysis The correlation coefficient between the SMRs in 1979–81 and 1984–86 was 0.50 ($P<0.001$). As a result of principal component analysis, 75% of the total variation of the SMRs was explained by the first principal component and the rest by the second principal component. Based on the first principal component value, 12 regions were classified into the high risk area, 23 regions into the medium risk area and 12 regions into the low risk area, as shown in Fig. 3. The results of one-way ANOVA between the three areas are shown in Table III. The variation between different risk categories was the largest in agriculture ($F=5.48$), followed by transport and communications ($F=4.03$) and tertiary industry (services, wholesale & retail and finance & insurance) ($F=3.75$). When the proportions were compared between two of three risk categories by means of Scheffe's F-test,[37] statistically significant differences were found between low and medium risk areas and between low and high risk areas in agriculture and between low and high risk areas in transport and communications.

DISCUSSION

The reliability of the attributable fractions determined in the present study depends on the summary RRs obtained from existing epidemiological data. Therefore, it is of primary importance to examine the appropriateness of using RRs of other countries to calculate summary RRs. An estimate of RR in an epidemiological study can vary due to a number of reasons in addition to the coincidental probabilistic fluctuation. An RR estimate may not represent the true RR of the study population due to certain problems in the study design or analytical methods. The term internal validity is used to refer to this problem.[38] On the other hand, the true RR among Japanese workers itself may differ from those in other countries because of certain differences in exposure status. The term external validity or generalizability is used to refer to this problem.[38]

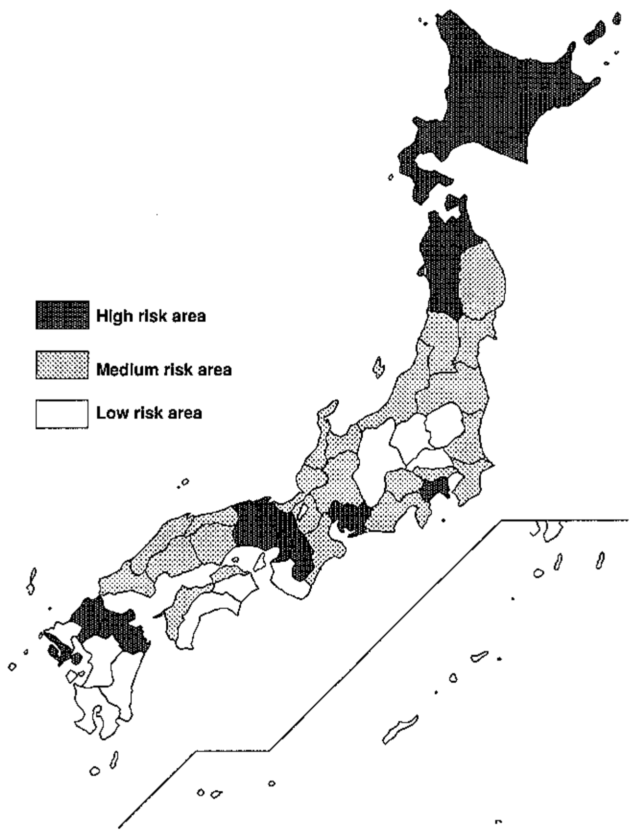

Fig. 3. The geographical distribution of bladder cancer deaths in male Japanese. The risk was evaluated by summarizing two standardized mortality ratios calculated for 1979–81 and 1984–86 using the principal component analysis.

For an estimate to be internally valid, confounding factors must be correctly controlled for in the study design or analysis. As confounding factors, age and gender are of primary importance. Cigarette smoking[2] should also be considered as a confounder if smokers are differentially distributed between the case and control groups. The age and gender were controlled for by matching or stratified analysis in all of the 27 case-control studies from which RRs were extracted. In 24 of them (89%), cigarette smoking was controlled for in the analysis stage by stratification or using statistical modeling techniques such as logistic regression. Race, residential area and beverage consumption were also considered in some studies. Thus, it can be concluded that RRs were not seriously biased to a degree which would render summary risk estimates unreliable.

The external validity of epidemiologic studies is often questioned when a meta-analysis is conducted using existing information. An ideal situation is to use an RR estimate obtained by a nationwide epidemiological study. Calculation of summary RRs from different population-based epidemiologic studies conducted in Japan may be the second best. However, since it is extremely difficult to find such estimates for various occupational risks, a surrogate had to be sought to enable an evaluation of occupational risks on a national basis. The RR of a certain occupational category may differ in different populations, even in the same country, if the exposure level

Table III. Comparisons of Workforce Distributions between 12 High Regions, 23 Medium Risk Regions and 12 Low Risk Regions by One-way Analysis of Variance

Industry	Low risk	Medium risk	High risk	F-test
Agriculture	0.138 (0.007)	0.095 (0.010)	0.076 (0.018)	5.48**
Manufacturing	0.190 (0.024)	0.239 (0.012)	0.215 (0.027)	1.74
Transport[a]	0.076 (0.003)	0.084 (0.002)	0.089 (0.003)	4.03*
Construction	0.142 (0.007)	0.137 (0.004)	0.132 (0.007)	0.60
Tertiary[b]	0.368 (0.007)	0.371 (0.009)	0.403 (0.010)	3.75*
Total	0.914	0.926	0.915	

a) Transport + communication.
b) Services + wholesale & retail + finance & insurance.
* $P<0.05$, ** $P<0.01$.

or exposure period is different from population to population. Faced with this situation, the best approach is to refer to as many epidemiologic studies as possible, each of which has high external validity. The number of cases, which was used as the weight in calculating summary RRs, can be considered to be a good indicator of the external validity in this sense. Cohort studies and nested type case-control studies were excluded for the same reason, since a risk estimate obtained from a cohort depends heavily on the work history of that cohort. For example, the SMRs or SIRs (standardized incidence ratio) of bladder cancer reported for workers in the petroleum industry ranged from 0.75 to 0.85,[39–41] lower than those of general populations, in striking contrast to the results of case-control studies.[10–16] This difference is presumably due to the difference in the exposure level and work history between the specific cohorts and the general populations studied.

The geographical distribution of bladder cancer mortality illustrated in Fig. 3 is unlikely to be explained by random fluctuations, since aggregations of both high risk and low risk regions were observed in several parts of Japan. The positive associations of bladder cancer mortality with proportions of employees in the transport/communications industry may be attributable to the elevated risk in drivers and mechanics as shown in Table I and Fig. 1. Alternatively, it may also be possible to relate the increased risk with urbanization and industrialization of the region and to regard the observed association as an indirect association. The positive association of bladder cancer risk with tertiary industry and the negative association with the agricultural industry seem to support the latter hypothesis. Further studies employing analytical epidemiological approaches to identify the association between bladder cancer incidence and a given occupation on an individual basis are needed to draw a conclusion regarding this question.

The estimated numbers of bladder cancer cases diagnosed in 1980, 4,643 in the total population and 2,885 among active employees aged 15 to 69, indicate that more than 60% of the total cases occurs among active workers and shows that preventive measures should be focused on this group. The estimated attributable fractions, 19% among active employees and 12% in the total population, further indicate that a preventive approach with regard to the high risk occupational group is of particular importance. Exposure to carcinogenic substances in the workplace is of primary interest. In addition to the sixteen chemicals and processes listed by IARC as human carcinogens, more than one hundred chemicals currently being used in various industries can be potentially carcinogenic to humans.[6] On the other hand, the results of geographical correlation analysis suggest that the risk of bladder cancer may increase as a result of urbanization and industrialization of a region. If this is true, changes in lifestyle including dietary habits and beverage consumption may also be contributing to the increased risk in high risk occupations. Two epidemiological studies conducted in Japan did not find any statistically significant increase in bladder cancer risk among workers in different industries.[42, 43] Thus, there may be differences in the level of occupational risks between Japan and other industrial countries and further epidemiological studies are required to evaluate the occupational risks in Japan. Effort must continue to be made to identify other unknown risk factors, occupational as well as non-occupational.

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APPENDIX

Suppose all male workers aged 15 to 69 are classified into those in occupational categories at high or low risk of bladder cancer. Letting P_k denote the proportion of workers in the high risk occupational category k among all workers, the incidence rate of bladder cancer in the entire workers can be formulated as the weighted average of occupation-specific incidence rates as follows:

$$I_p=(1-\sum_j P_j)\times I_0+\sum_j P_j\times I_j, \quad \text{(a1)}$$

where I_p and I_0 are the incidence rates in the entire population and in the low risk population, standardized to the age structure of occupational category k, and I_j the incidence rate in workers of the high risk occupational category j. Further, letting RR_k denote the relative risk in occupational category k as compared to low risk workers,

$$I_j=RR_j\times I_0. \quad \text{(a2)}$$

Equation (a1) can be modified by using formula (a2) as follows:

$$I_p=(1-\sum_j P_j))\times I_0+\sum_j P_j\times RR_j\times I_0. \quad \text{(a3)}$$

Solving equation (a3) for I_0,

$$I_0=\frac{I_p}{1-\sum_j P_j+\sum_j P_j\times RR_j}. \quad \text{(a4)}$$

Further applying (a2) to (a4),

$$I_k=\frac{RR_k\times I_p}{1-\sum_j P_j+\sum_j P_j\times RR_j}. \quad \text{(a5)}$$

The fraction of bladder cancer attributable to high risk occupations can be formulated using equation (a5) as follows:

$$AF=\frac{I_p-I_0}{I_p}=\frac{\sum P_j\times RR_j-\sum P_j}{1-\sum_j P_j+\sum_j P_j\times RR_j}.$$

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