TEMPORAL ASPECTS OF OCCUPATIONAL BLADDER CARCINOGENESIS

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Abstract Temporal aspects of occupationally induced bladder cancer were estimated with data from a case-control study in eastern Massachusetts. A total incidence series of men with bladder cancer were the cases, and an age-matched sample of men selected at random from the general population were the controls. The younger a man is when he begins employment in a hazardous occupation, the higher his risk of bladder cancer. Men first employed in a hazardous occupation by the age of 25 have a risk 2.4 times that of men never so employed. Virtually no excess risk is apparent for men first employed in such occupations after the age of 25. Risk of occupational bladder cancer is greatest 41 to 50 years after beginning employment in a hazardous occupation, the "latent period." There is no change in risk with increasing duration of employment in such occupations. However, it appears that increased duration of employment in a hazardous occupation is associated with a shortened latent period. (N Engl J Med 288:1040-1043, 1973)

TEMPORAL aspects of human carcinogenesis, such as variation in susceptibility with age at exposure, have been well studied for cancers induced by radiation and cigarette smoking. However, little information relates to chemical carcinogenesis in man despite the burden of human cancer for which chemicals are thought responsible.[1] The causal association of certain occupational exposures with bladder cancer provides an example of chemical carcinogenesis that can be studied in man. We have used information from a study of the epidemiology of bladder cancer to describe several temporal characteristics of the occupationally induced disease.

METHODS

Study Design

The study methods have been described in detail elsewhere.[2,3] Briefly, this was a case-control study of lower-urinary-tract cancer that included as cases all persons who were newly diagnosed during an 18-month period as having transitional or squamous-cell carcinoma of the renal pelvis, ureter, bladder or urethra, and who resided in a defined area in eastern Massachusetts. Since 94 per cent of these patients had a bladder tumor, the term bladder cancer is used to refer to all lower-urinary-tract cancers. For each case, a control subject of the same sex and age was selected at random from a roster that comprised a random sample of all adults in the study area stratified for age and sex. A sample of cases and of controls was asked to grant an interview.

The emphasis of the interview was on lifetime smoking habits and occupation after the age of 12. A positive association between disease and cigarette smoking was demonstrated.[2] Employment in certain occupations was also identified as a risk factor.[3] Since the occupation associations were essentially limited to men, this report is restricted to 347 male patients and 364 male controls who provided complete occupation histories. This is 90.1 per cent and 88.3 per cent of the respective samples asked for an interview. Nine interviewed patients and 10 controls were excluded because data of specific interest were unavailable.

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Occupation

A "hazardous" occupation is defined as one for which there was a priori reason to believe that increased risk of bladder cancer exists and for which increased risk was demonstrated in our prior report.[3] These occupations involve work in the rubber industry and the leather industry, and work with dyestuffs, paint and other organic chemicals. A man was classified as having worked in a hazardous occupation if he had held a position in one of these industries for six months or longer. Initial analyses of the variables presented were done for each of four industry groups — leather, rubber, "other hazardous" and multiple hazardous occupations. Findings for the groups were similar, so that all hazardous occupations were merged for most of this presentation.

Three variables were investigated. "Age-at-Starting" is the age of a subject when first employed in a hazardous occupation. "Latent Period" is the number of years elapsing between the age-at-starting and the age at inclusion in this study. "Duration" is the total years of employment in hazardous occupations.

Analytic Methods

The measures of effect used in this analysis are the crude risk ratio and the standardized risk ratio of Miettinen.[4] All ratios presented are relative to a risk of 1 for men never employed in a hazardous occupation. Standardization was done to assess the association of bladder-cancer risk with each temporal variable, independently of the others and also to control differences between the case and control distributions in current age, cigarette smoking and categories of hazardous occupations.

The tests of significance used are those described by Mantel and Haenszel[5] and Mantel[6] and are presented only for the associations of risk with age-at-starting. The data for latent period and duration were grouped to reflect best the trends that seemed valid on the basis of the ungrouped data, and such a posteriori grouping renders significance tests inappropriate.

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Results

Age-at-Starting

The association of bladder-cancer risk with age-at-starting employment in a hazardous occupation is shown in Table 1. The highest risk ratio, 4.8, is incurred by men with the youngest age-at-starting. Risk declines steadily for each successive age-at-starting category until little excess risk is demonstrable for men who began work in a hazardous occupation after the age of 25. Even excluding the unexposed, this trend is statistically significant ($p<0.02$). Table 2 shows this association to be similar for each category of hazardous industry.

The association with age-at-starting was investigated with standardization for age at diagnosis, for the calendar year in which exposure began, for duration of work in a risk occupation, for cigarette smoking and for several combinations of these variables. The risk ratio for each age-at-starting group was essentially unchanged by these procedures. For example, standardization both for calendar year of first exposure and for duration of exposure yielded risk ratios of 2.4 for the 12-to-25 age-at-starting level and 1.2 for the 26+ category. The difference between these two risks is statistically significant ($p<0.03$).

The subsequent analyses were done first for all subjects and then repeated with restriction to men with age-at-starting less than 26. The associations noted were similar, the restriction resulting only in uniformly higher risks and more consistent trends. This result is to be expected if men exposed after the age of 25 do not acquire disease as a result of occupational exposure. The remainder of this report, therefore, is restricted to men first exposed before the age of 26.

Latent Period

Bladder-cancer cases and controls categorized by latent period are presented in Table 3. Excess risk appeared in each category, rising to a maximum in the period from 41 to 50 years and then declining. This association remained unchanged with standardization for age-at-starting, cigarette smoking or current age. However, further investigation of this association revealed what appeared to be different trends for different durations of exposure (Table 4). Some regrouping was necessary to maintain adequate numbers in each cell. Among men employed in a hazardous occupation for a relatively short period, up to 10 years, the risk ratio increases with increasing latent period. For men employed for more than 10 years, the highest risk ratio occurs within the first 40 years and then declines. If these trends are valid, highest risk for men with an intermediate duration of hazardous employment should occur at an intermediate latent period. The data, upon further subdivision, are compatible with this, but observations are too few to be definitive.

Table 1. Number of Cases and Controls and Risk Ratio According to Age when Employment in a Hazardous Occupation Began.*

Age-at-Starting (Yr)	Cases	Controls	Risk Ratio†
12-15	26	10	4.8
16-20	57	30	2.5
21-25	22	16	2.0
26-35	11	14	1.1
36+	14	17	1.3
Never	217	277	1.0

*$\chi^2 = 6.0$ $p< 0.02$, excluding "never" category.
†Standardized over 3 categories of hazardous occupation.

Table 2. Number of Cases and Controls and Risk Ratio According to Age when Employment in a Hazardous Occupation Began, for Three Categories of Hazardous Industry.*

Industry	Age-at-Starting (Yr)	
	12-25	26+
Leather:		
Cases	48	8
Controls	18	7
Risk ratio	3.4	1.5
Rubber:		
Cases	23	7
Controls	17	11
Risk ratio	1.7	0.8
"Other hazardous":		
Cases	24	10
Controls	14	13
Risk ratio	2.2	1.0

*10 cases & 7 controls with exposures in multiple categories are excluded.

Discussion

The decreasing risk of bladder cancer with increasing age at first exposure to a hazardous occupation is perhaps the most interesting of the present results. The few comparable data are contradictory. Most relevant to the current investigation is the report by Case et al.[7] on bladder tumors among dyestuffs workers, in which a significant association of increasing risk with increasing age at first exposure was found. An explanation for

Duration

One measure of "dose" of carcinogen available in a case-control study of occupational hazards is the duration of employment in risk occupations. This measure is particularly useful when several different occupations are considered as a group. Table 5 illustrates the association of bladder-cancer risk with this variable. As can be seen, no trend is evident. The pattern remains unchanged when standardized for age-at-starting and for cigarette smoking.

Table 3. Number of Cases and Controls and Risk Ratio According to the Number of Years Elapsing between First Employment in a Hazardous Occupation and Diagnosis (Latent Period).*

Latent Period (Yr)	Cases	Controls	Risk Ratio
≤30	11	8	1.8
31-40	19	10	2.4
41-50	39	13	3.8
51+	36	25	1.8

*Excluded are 25 cases & 31 controls with an age-at-starting of 26 yr or more.

Table 4. Number of Cases and Controls and Risk Ratio According to Latent Period, in Two Duration-of-Exposure Groups.*

Duration of Work in Risk Occupations (Yr)	Latent Period (Yr)		
	≤40	41-55	56+
≤10:			
Cases	16	19	17
Controls	13	10	5
Risk ratio	1.6	2.4	4.3
11+:			
Cases	14	28	11
Controls	5	15	8
Risk ratio	3.6	2.4	1.8

*See footnote to Table 3.

these conflicting observations may be that the authors studied a different and overwhelmingly carcinogenic exposure. There are also reports of increased risk of leukemia, lung cancer and cancer of the nasal sinuses with older age at first exposure to ionizing radiation, asbestos and nickel, respectively.[8,9] On the other hand, the association of age at first exposure with risk presented here is similar to that reported for several radiation-induced cancers[10-12] and lung cancer induced by cigarette smoking.[13]

These apparent contradictions may result from methodologic difficulties as well as biologic differences. Specifically, in the analysis of age-at-starting the effects of two relevant variables, latent period and age at diagnosis, cannot be controlled simultaneously. This is because each of the variables is a linear combination of the other two — i.e., age at diagnosis equals age-at-starting plus latent period. If the association of bladder-cancer risk with age-at-starting were to differ depending on which of the other two variables is controlled, the problem would arise about which association reflects reality. In the present data, the association of risk with age-at-starting is similar with control for either of the two other variables.

There are explanations for the relation of increased cancer risk with younger age at first exposure other than an increased susceptibility of younger organisms. It may be that when a young person enters a hazardous industry, he is likely to be given a job involving harmful exposures. Case et al. suggested the converse of this to explain their finding of higher risk with older age at first exposure. They speculated that older men, considered more responsible and careful, were preferentially assigned to handle the potentially dangerous chemicals.

We cannot say there is no risk of occupation-induced bladder cancer if exposure begins after the age of 25. But a practical implication of our finding, if corroborated, is that potentially carcinogenic industrial exposures should be restricted to older men until the hazard has been evaluated.

Table 5. Number of Cases and Controls and Risk Ratio According to Duration of Employment in Hazardous Occupations.*

Duration (Yr)	Cases	Controls	Risk Ratio
≤5	39	19	2.6
6-10	13	9	1.8
11-30	27	12	2.9
31+	26	16	2.1

*See footnote to Table 3.

The apparent relation of bladder-cancer risk with latent period may reflect only changes in exposure occurring with time. This is because all the cases were newly diagnosed during a short interval (18 months). For example, the category of 41-to-50-year latent periods designates exposures started between 1917 and 1926. However, the association of risk with this variable seems more compatible with the concept of latent period than with secular change. If there were a trend over time in the utilization of harmful chemicals in these industries, one would not anticipate it to have been similar in all three categories of risk industries. Furthermore, a secular trend would probably be consistently increasing or decreasing, not increasing and then decreasing. Although such fluctuations in exposures could occur, a more likely explanation of the observed distribution of latent periods is that it reflects the distribution of incubation periods typical of human disease. Case et al. noted a rise and fall in the distribution of latent periods among men in their study and demonstrated that this was indeed a function of incubation period rather than a change in types of exposure with time. With either interpretation, however, the fact is that exposures sustained over 30 years ago are now producing bladder cancer.

Finally, although the data are not firm, the inverse relation between duration of exposure and length of latent period is as one might predict. It is generally observed in experimental carcinogenesis that the duration of the latent period is inversely related to the amount of carcinogen administered.[14-16] Furthermore, Case et al. demonstrated that the more potent the carcinogen, the shorter the latent period for bladder cancer in man. They suggested that the same pattern might hold when considering the duration of exposure to hazardous agents, but it did not in their data. There is some indication in the present study, however, that this temporal feature of experimental carcinogenesis applies to man. The presence of this association and the absence of any trend in the risks in Table 5 suggest the idea that once a man has experienced a relatively small dose, further exposure does not increase risk but does shorten latent period. This could be explained by a threshold phenomenon and the observation that many chemicals that act as initiators of cancer also act as promoters.[1]

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