Fede Asbestos J Chem MEY-3

Environmental Research
Volume 42, Number 2, April 1987

CONTENTS

Continued on inside back cover

ENVIRONMENTAL RESEARCH 42, 353–361 (1987)

Asbestos and Renal Adenocarcinoma: A Case–Control Study

MALCOLM MACLURE

Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115

Received February 12, 1986

A case–control study of renal adenocarcinoma has corroborated the hypothesis that asbestos is a cause of the disease. The odds of having been moderately or heavily exposed to asbestos 30 years before diagnosis were 45:473 among cases, whereas the comparable odds among controls were 26:492. A matched-pair analysis yielded an exposure odds ratio of 1.8 with 95% confidence limits of 1.1 and 3.1. After controlling for potential confounders and selection factors by means of logistic regression, the incidence rate ratio was estimated to be 1.6, with a one-sided 95% confidence limit of 1.0.

INTRODUCTION

The hypothesis that asbestos may be a cause of renal adenocarcinoma was first corroborated when Selikoff and colleagues (1979) reported that their continuing follow-up of 17,800 insulation workers had revealed 18 kidney cancer deaths when only 8.1 were to be expected. As always, the result could have been due to chance. Alternatively an unrecognized source of incomparability between the insulation workers and the standard US white male population may have introduced confounding. Coupled with evidence (Langer, 1974) that asbestos fibers can spread throughout the body, however, the rate ratio of 2.2 suggested causality. We were in a position to test this hypothesis further in a case–control study of renal adenocarcinoma conducted in eastern Massachusetts where a substantial number of people were at one time employed in shipyards.

METHODS

During the period 1981–84, 1190 cases of renal adenocarcinoma were identified from the records of 37 participating hospitals in an area around Boston comprising some 100 townships. Patients who were diagnosed before 1976 or before age 30, or who did not reside in the specified geographic area, were formally ineligible. Of those formally eligible, 30% were deceased, and 24% were not interviewed at their own, their physicians', or their families' requests, or because they had moved. Of the 549 interviewed cases, 31 were excluded from the following analyses because of mismatches with controls in age, because of poor quality interviews, or because they or their controls were nonwhite. The representativeness of the interviewed cases was judged by comparing abstracts of their medical charts with comparable information from the charts of noninterviewed cases.

Each of the 518 interviewed cases was matched with a control of the same age and sex systematically selected from the case's precinct of residence using the

0013-9351/87 $3.00

annually updated residence lists of Massachusetts towns. For any case under 50 years of age, a second control was selected and interviewed, so as to compensate for the small number of young cases. Whenever a control declined to participate (45% of the time), an alternative match was selected by the same procedure. Information was obtained from 60% of the noninterviewed controls by means of a short mail questionnaire. Detailed analyses of potential sources of selection bias based on data from this questionnaire and from the cases' medical records are to be presented elsewhere (in preparation).

The hour-long interview encompassed a wide range of topics in addition to occupational history, including past intake of foods and beverages, use of drugs and vitamins, smoking and exercise, disease history, and ethnicity. Detailed questioning on occupations was therefore ruled out. Furthermore, asbestos was only one among a number of hypothesized occupational risk factors investigated. Nevertheless, occupational history was the first major section of the interview, and the word "ASBESTOS" in 1 cm capitalized letters topped the list of substances on the card handed to the interviewees when they were asked about specific exposures. Subjects were therefore at their most alert when asked about jobs and could not have missed the opportunity to mention exposure to asbestos. With concern for the possibility of biased reporting by cases. due to increasingly widespread knowledge of the carcinogenicity of asbestos and other substances, open-form questions about occupational history were asked first, and lists of industries and substances were only afterwards given to the subjects to supplement their accounts.

In the course of coding, data entry, and verification of the interview data, evidence was found of underreporting and overreporting of asbestos exposure. The open-form questions on occupational history revealed that many people who did not report asbestos exposure had had jobs in which they almost certainly were exposed: 43 shipyard workers, several boilermakers, and a steamfitter. On the other hand, among those who reported continual exposure to asbestos, there were five mechanics, five firefighters, three teachers, and a variety of others whose intensity of exposure was arguably much lower. Apparently self reports of exposure to asbestos could not be wholly relied upon. At best, they could be taken only as supplementary information on specific occupations.

A list of all subjects who might have been exposed to asbestos was therefore prepared. Anyone who mentioned exposure to the substance, who reported employment in the shipbuilding industry, or who was a pipefitter, steamfitter, or boilermaker was included in the list. Using all available information from the interview, each subject on the list was categorized as having "high," "intermediate," "low," or "negligible" exposure by two colleagues well versed in the idiosyncracies of asbestos distribution in the workplace. Their judgements were made independently without knowing whether a subject was a case or a control.

The rate ratio was estimated by means of the exposure odds ratio (EOR) which, in the matched-pair analysis, was computed as the ratio of the number of discordant pairs in which the case was exposed to the number in which the control was exposed (Fleiss, 1981). In the stratified analyses, the Mantel–Haenszel estimator of the EOR was used (Mantel and Haenszel, 1959). In the multivariate analysis,

Continued from outside back cover

the EOR was computed as the antilog of the coefficient from a conditional logistic regression (Breslow and Day, 1980). Since only 6 of the 87 second controls matched with cases under age 50 had reported exposure to asbestos, all of it recent because they were young, these subjects added little but complexity to the presentation of the data. For clarity, therefore, they were excluded from all figures and tables shown below and all analyses except the overall logistic regression. The full analysis and interpretation of the logistic model is to be presented elsewhere (in preparation).

RESULTS

There were 79 subjects rated by both reviewers as intermediate or high in exposure, 24 rated by only one reviewer as intermediate or high, and 38 subjects who reported exposure to asbestos but were rated by both reviewers as low or negligible in exposure. In recognition of the inevitable subjectivity of any exposure rating scheme, as well as the rarity of opportunities to test this etiologic hypothesis and the diverse ways in which epidemiologic data on asbestos exposure are used, we have chosen to present the raw data on all 141 subjects in Figs. 1 and 2, allowing readers to scrutinize them critically and to reanalyze them with alternative rating schemes.

The figures show the distribution of exposure years for cases and controls in a manner which permits visual assessment of the EOR while allowing an induction period of any length to be assumed. Each horizontal line traces a single subject's years of exposure across the decades preceding his or her diagnosis of renal cancer or, for a control, preceding the date when his or her matched case was diagnosed. Figure 1 shows the exposure years of subjects rated intermediate or high by either of the reviewers. Figure 2 shows the reported exposure years of subjects who were rated by both reviewers as having had low exposure.

Table 1 is a condensation of Fig. 1 showing the numbers of cases and controls rated as intermediate or high in exposure by both reviewers. The numbers are stratified by the decade when the subject was first moderately or heavily exposed, counting backwards from the date of the case's diagnosis. The corresponding crude EORs are shown. Since exposure within three decades of diagnosis appeared no more common among the cases than among the controls (EOR = 1), a 30-year induction period was assumed.

The operational definition of exposure adopted for all subsequent analyses was agreement by both reviewers that the subject had had intermediate or high exposure to asbestos at least 30 years prior to the date of the case's diagnosis. Based on this definition, there were three concordant pairs: matched-pair numbers 03, 09, and 34 in Fig. 1. (Matched-pair number 35 was counted as discordant since the control's exposure was recent.) There was little correlation of cases' and controls' exposures due to matching (correlation coefficient = 0.02), but matched analyses were done since the data in Fig. 1 lend themselves to such an approach.

The discordant pair ratio was 42:23 meaning the EOR was 1.8 with 95% confidence limits of 1.1 and 3.1 (Fleiss, 1981). Mantel–Haenszel estimates of the EOR from an analysis of the unmatched data, stratified by age, sex, and either years of

FIG. 1. Chronologic distribution of cases' and controls' years of moderate or heavy exposure to asbestos, dated in years prior to cases' dates of diagnosis. Key: 22222, rated heavy to moderate by both reviewers; 11111, rated heavy to moderate by only one reviewer; 00000, rated as light or negligible by both reviewers; (25), subject claimed exposure 25 hr/week; (40), exposed 40 hr/week or "all the time"; (?), reported exposure but did not quantify; (-), subject did not report asbestos exposure; [n], never smoked; [x], quit smoking 10 years before diagnosis; [m], smoked up to 1 pack/day within 10 years of diagnosis; [h], smoked more than 1 pack/day within 10 years of diagnosis.

schooling, or socioeconomic rank of the most recent occupation according to the Standard Occupation Classification Manual (US Dept. Commerce, 1980), were no different. From a conditional logistic regression, controlling for known renal cancer risk factors (history of smoking, obesity, and kidney stones) as well as

Continued from outside back cover

KOICHI KONO, YASUHISA YOSHIDA, HIROSHI YAMAGAT...

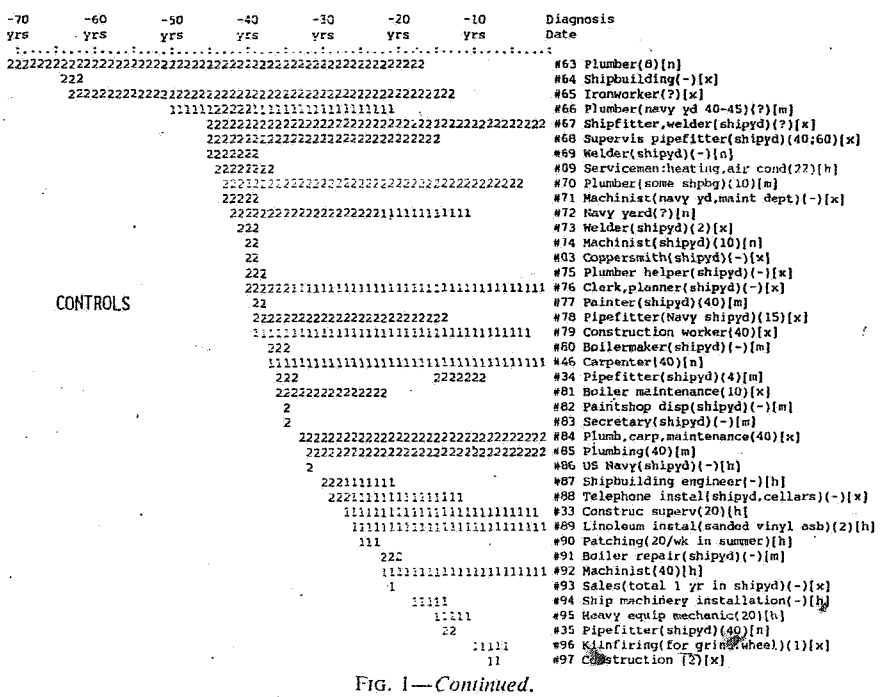

FIG. 1—*Continued.*

other hypothesized risk factors and potential selection biases (hypertension, phenacetin, dietary protein, years of schooling, income, and status of recent job), the EOR was estimated to be 1.6 with a one-sided 95% confidence limit of 1.0.

The hypothesis that smoking modifies the association of asbestos with renal adenocarcinoma was tested by stratifying the study population by smoking history as shown in Table 2. The definitions of smoking subcategories in Table 2 are the same as the definitions used in Figs. 1 and 2. (The smoking status of each subject is indicated in the figures by the letter n, x, m, or h in brackets, referring to "never smoked," "exsmoker 10 years before diagnosis," "moderate or light smoker," and "heavy smoker," respectively.) Table 2 shows that asbestos-exposed cases outnumbered asbestos-exposed controls mainly in two categories—never smoked and recent heavy smokers. By contrast, among exsmokers and recent moderate smokers, the odds of asbestos exposure were very similar for both cases and controls. The lack of a smooth trend in the odds ratios across smoking categories is readily explicable in terms of the instability of each odds ratio. Indeed the large odds ratio among heavy smokers appears to be mainly due to the low odds of asbestos exposure among heavy smoking controls, rather than to an unusually high exposure odds in the cases. The wide confidence intervals around the odds ratios, even after grouping all smokers together, preclude rigorous testing of the hypothesis that smoking modifies an asbestos effect.

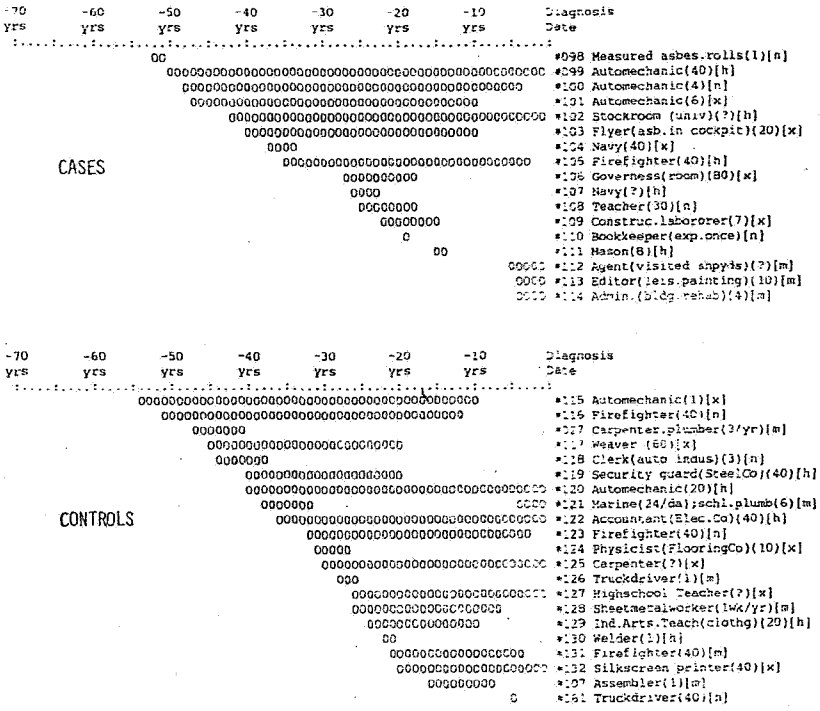

FIG. 2. Chronologic distribution of reported years of asbestos exposure for subjects judged as having had light or negligible exposure, dated in years prior to cases' dates of diagnosis. See Fig. 1 for key.

DISCUSSION

There are four alternatives to an etiologic explanation for the observed association between asbestos and renal adenocarcinoma: random sampling variation, selection bias, information bias, and confounding.

By the conventional criterion of the 95% confidence interval excluding the null, sampling variation can be virtually ruled out as an explanation. In doing so, no account is taken of probable but unquantifiable nondifferential random error in classifying subjects with regard to exposure. This would only cause underestima-

TABLE 1

DISTRIBUTION OF EXPOSED SUBJECTS BY DECADE WHEN THEY FIRST BECAME MODERATELY OR HEAVILY EXPOSED, ACCORDING TO BOTH REVIEWERS

	Time of first exposure (*in decades before case's diagnosis*)				
	6–8	5	4	1–3	Total
Cases	2	11	32	4	49
Controls	3	9	14	4	30
Crude exposure odds ratio	0.7	1.2	2.4	1.0	

Continued from outside back cover

KOICHI KONO, YASUHISA YOSHIDA, HIROSHI YAMAGATA,

TABLE 2
ODDS OF ASBESTOS EXPOSURE 30 YEARS BEFORE CASE'S DIAGNOSIS, AFTER STRATIFYING BY SMOKING HISTORY

	Asbestos exposure odds (exposed:nonexposed)		Crude odds ratio	95% Confidence interval
	Cases	Controls		
Never smoked	11:174	4:187	2.9	(1.0, 8.9)
Ever smoked	34:298	22:305	1.6	(0.9, 2.6)
Exsmokers (quit 10 years+)	14:114	12:114	1.2	(0.5, 2.6)
Recent moderate[a] smokers	8:94	8:103	1.1	(0.4, 2.9)
Recent heavy[b] smokers	12:90	2:88	5.9	(1.4, 24.)

[a] One pack per day or less, within 10 years of case's diagnosis.
[b] More than one pack per day, within 10 years of case's diagnosis.

tion of both the point and interval estimates. Any adjustment for such random misclassification would only make sampling variation seem less likely as an explanation. Moreover, one might consider that the definition of exposure was overly restrictive and increased the problem of sampling variation by reducing the number of subjects classified as exposed. Repeating the above analyses using the more inclusive criterion—that a subject must be rated as moderately or heavily exposed by at least one reviewer, rather than by both—one obtains an odds ratio of 2.0 (95% confidence limits: 1.2 and 3.4) from the matched-pair analysis and an estimate of 1.8 (95% confidence limits: 1.1 and 3.1) from the logistic regression.

The possibility of selection bias was studied by multivariate analyses of data abstracted from medical records of interviewed and noninterviewed cases, and of data from controls' interviews and mail questionnaires returned by noninterviewed controls. These analyses showed that the main selection factors which might have biased a crude analysis were education, current socioeconomic status, cardiovascular disease, and age. These factors were partially controlled by the matched-pair design and analysis, and any residual selection bias was further controlled by stratified analyses and conditional logistic regression (Kleinbaum, Kupper and Morgenstern, 1982). The lack of substantial differences among the EOR estimates from crude, stratified and multivariate analyses indicates that selection bias, at least by these factors, is an unlikely explanation.

If the subjects' own reports of asbestos exposure had been taken as the operational definition of exposure in the analyses, there would have been opportunity for positive information bias due to some of the cases having read more about the causes of cancer and thought more about their past exposures. The data show, however, that if this happened in a few instances, it would have been more than obscured by the negative information bias due to the above-mentioned nondifferential misclassification. Figure 2 lists all the subjects who, it might be said, overreported asbestos exposure insofar as both reviewers rated their exposure as low or negligible in intensity. It can be seen that controls overreported exposure as often as cases. To reduce such misclassification, self-reported exposure served only as a criterion for inclusion on the shortlist of subjects whose occupational data was to be screened by the reviewers. As it turned out, the major contribution

to the operational definition of exposure was employment in shipyards and people so employed more often than not denied ever being exposed to asbestos. Therefore information bias is a very unlikely explanation for the association. Such a conclusion is consistent with the results of a psychological study of mesothelioma patients by Lebovits and colleagues (1983) who found most patients believed their asbestos exposures had not contributed to their getting the disease.

The hypothesis that the association was wholly or partially due to confounding by other renal cancer risk factors was tested by multivariate analyses using a wide variety of combinations and transformations of variables encompassing smoking history, nutrient intake, ethnicity, drug use, and disease history. The asbestos exposure odds ratio estimates from these models remained in the range 1.5 to 2. This does not eliminate the possibility that unknown risk factors, or suspected risk factors measured imperfectly and therefore only partially controlled, might account for the association. For example, exposure to lead and other metals also occurs in many of the jobs listed in Fig. 1. Separate analyses of the data on lead and metal exposure, however, tended to refute the hypotheses that they are risk factors. On balance, confounding appears an insufficient explanation for the association with asbestos.

Insofar as the evidence disfavors the four alternative explanations, it corroborates the hypothesis that asbestos is a cause of renal adenocarcinoma. The kidney was the first site outside the digestive and respiratory tracts in which a significant excess of fatal cancers occurred among Selikoff's insulation workers, so there was reason to be skeptical of a causal interpretation. Such an interpretation would have been especially untenable if asbestos fibers could not be shown capable of reaching the kidney. Laboratory experiments with mice and rats, however, demonstrate that asbestos fibers can be widely disseminated by means of the lymphatic pathways and the circulation (Kanazawa *et al.*, 1970; Sebastien *et al.*, 1980). The same process is inferred to occur in humans since autopsies of asbestos workers have revealed asbestos bodies in various organs remote from the respiratory and digestive systems (Langer, 1974). Among the remote organs, the kidney was the one in which Langer observed the highest concentrations of asbestos bodies. Moreover, asbestos fibers have been found in human urine (Cook and Olson, 1979). It seems likely, therefore, that many of the people in the present study, who reported working in shipyards 30 years ago, harbor asbestos fibers in their kidneys today. Whether it is only because these people were exposed to much higher dust levels back then, or whether asbestos fibers need 20 years or more to manifest their carcinogenicity in the renal parenchyma, the timing of their exposures appears to have been important. The lack of an association with recent asbestos exposure, which was the basis for the working assumption of a 30-year induction period in the analysis, adds support to a causal interpretation by further disfavoring selection bias and information bias as explanations; biasing factors would tend to be associated with recent exposures more than with exposures in the distant past. A further test of the causal hypothesis was to examine the data for evidence of modification by smoking. However, when the study population was subdivided into four strata by smoking history,

the odds ratios
hypothesis.
The analyses
defined in this
adenocarcinom
carcinoma whic
diagnoses, to a
1940s and early
clusion lies rigl
used in toxic tc
was "as likely

I am very gratel
Godfredsen, Mich
ported by a grant
fellowship from th

Breslow, N. E., a
Publ. 32.
Cook, P. M., and
204, 195–198.
Fleiss, J. L. (198
Harter, P. J. (198
Issues." Mor
Washington.
Kanazawa, K., B
from subcuta
Kleinbaum, D. G
and Quantita
Langer, A. M. (1
ease. *Enviro*
Lebovits, A. H.,
responses of
Mantel, N., and
studies of di
Sebastien, P., M
intestinal lyr
Selikoff, I. M., F
in the Unite
U.S. Dept. Com
Publ. No. 8(

Continued from outside back cover

the odds ratios were too imprecise to provide further evidence for or against the hypothesis.

The analyses presented here suggest that asbestos exposure, as operationally defined in this study, causes a 50 to 100% increase in the incidence rate of renal adenocarcinoma. The data suggest that as many as half the cases of renal adenocarcinoma which occur among people who were exposed, 30 years before their diagnoses, to asbestos levels comparable to those in US shipyards during the 1940s and early 1950s may be attributable to their asbestos exposures. This conclusion lies right on the borderline of the "preponderance of evidence criterion" used in toxic tort law, namely, that evidence should indicate a claimant's disease was "as likely as not" due to the exposure in question (Harter, 1984).

ACKNOWLEDGMENTS

I am very grateful for the advice of Charles Poole and wish to thank him, Ronald Bruno, Morag Godfredsen, Michael Ellenbecker, and Rebecca Kolodny for their contributions. This work was supported by a grant from the National Cancer Institute (5 R01 CA29723) and partially supported by a fellowship from the DuPont Company, Wilmington, Delaware.

REFERENCES

Breslow, N. E., and Day, N. E. (1980). "Statistical Methods in Cancer Research." Vol I., IARC Sci. Publ. 32.

Cook, P. M., and Olson, G. F. (1979). Ingested mineral fibers: Elimination in human urine. *Science* 204, 195–198.

Fleiss, J. L. (1981). "Statistical Methods for Rates and Proportions." 2nd ed. Wiley, New York.

Harter, P. J. (1984). The dilemma of causation in toxic torts. *In* "Selected Studies in Health Policy Issues." Monograph 101. Institute for Health Policy Analysis, Georgetown Univ. Med. Center, Washington, D.C.

Kanazawa, K., Birbeck, M. S., Carter, R. L., and Roe, F. J. C. (1970). Migration of asbestos fibers from subcutaneous injection sites in mice. *Brit. J. Cancer* 24, 96–106.

Kleinbaum, D. G., Kupper, L. L., and Morgenstern, H. (1982). "Epidemiologic Research: Principles and Quantitative Methods." Wadsworth, Belmont, Calif.

Langer, A. M. (1974). Inorganic particles in human tissues and their association with neoplastic disease. *Environ. Health Perspect.* 9, 229–233.

Lebovits, A. H., Chahinian, A. P., and Holland, J. C. (1983). Exposure to asbestos: Psychological responses of mesothelioma patients. *Amer. J. Ind. Med.* 4, 459–466.

Mantel, N., and Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl. Cancer Inst.* 22, 719–748.

Sebastien, P., Masse, R., and Bignon, J. (1980). Recovery of ingested asbestos fibers from the gastrointestinal lymph in rats. *Environ. Res.* 22, 201–216.

Selikoff, I. M., Hammond, E. C., and Seidman, H. (1979). Mortality experience of insulation workers in the United States and Canada, 1943–1976. *Ann. N. Y. Acad. Sci.* 330, 91–116.

U.S. Dept. Commerce (1980). "Standard Occupation Classification Manual." U.S. Govt. Print. Off. Publ. No. 80-332-946, Washington, D.C.