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June 25, 1981

A Review of:

In Reply
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personal use only and may not be
quoted or cited until it is publicly
available *R. T. Shellen*
Waxweiler, RJ, Smith, AH, Tyroler, HA and Falk, H "An epidemiologic
investigation of an excess lung cancer risk in a synthetic chemicals slant"
XIX International Congress on Occupational Health; Dubrovnik, Yugoslavia (1978)

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This paper is the partial report of studies conducted at a chemical manufacturing plant in Louisville, Kentucky. The text appears to be part of a larger manuscript, perhaps an unpublished Ph.D. dissertation. A related study that pertains to some of the workers described in this particular report, appeared as part of the proceedings of an occupational health conference (Annals of the New York Academy of Sciences, Vol. 271, pp 40-48, 1976). Correspondingly, a portion of the methodologic aspects of the paper (the serially additive expected dose model) was published in an epidemiologic journal (American Journal of Epidemiology, Vol. 112, pp 787-797, 1980). A search of the index medicus did not reveal any other publication by these authors concerning this particular study. Our review is confined solely to the paper at hand.

The paper describes three separate but related lines of investigation. The first is a study, based on historical information, of the respiratory cancer mortality among workers in the Louisville plant. The second compares the histology of lung cancers among deceased workers with the histology of lung cancers seen among a selected group of non-factory workers. The third consists of a comparison of the cumulative exposure to chemicals among workers deceased with lung cancer as opposed to the exposures among a selected group of workers who did not die of lung cancer. We will consider each of these investigations with regard to its epidemiologic method and findings separately.

PART ONE -- RESPIRATORY CANCER MORTALITY STUDY

The study of respiratory cancer mortality among factory workers used a traditional historical cohort design. All persons employed at the plant

between 1942 through 1973 comprised the cohort. The investigators traced these persons and obtained death certificates for those known to have died. The period at risk of death was calculated using a standard technique, with person months at risk stratified by five year age group, calendar time, and latency. The calculation of expected deaths was based upon U.S. white male mortality rates.

This analysis resulted in a standardized mortality ratio (SMR) of 149, that is, the respiratory cancer mortality for all workers in the plant was 1.49 times what would be expected among the total U.S. population of white males. The elevated SMR persisted when the analysis was confined to those individuals who died a minimum of ten years after their first day of work in the plant. The excess of deaths for all plant workers was similar to that reported earlier among the subgroup of vinyl chloride workers in this plant.

CRITIQUE

The study method employed to calculate the standardized mortality ratio is an acceptable and widely used technique in occupational health studies. Completeness of follow-up among the cohort is a goal with this approach. In this study 4,806 subjects were eligible for the cohort and only 73 were lost to follow-up. This degree of follow-up, 98%, therefore, is excellent.

The investigators chose for their comparison the mortality experience of all U.S. white males. This choice can affect the interpretation of study results. Respiratory cancer mortality varies considerably among different

geographic regions of the U.S.; occupational health exposure may account for a part of this heterogeneity, but certainly not all. Regional differences in smoking habits and air pollution levels may explain other components of the variation. During the period 1950-1969 Jefferson County, Kentucky, in which Louisville is located, reported 1,901 deaths among white males due to respiratory cancer. The age-adjusted respiratory cancer mortality for white males in this county was 16% higher than that for all U.S. white males during those years. Excess deaths from lung cancer among workers in the plant under study could have contributed only minimally to the reported excess for Jefferson County. The one and one-half fold excess of respiratory cancer mortality among factory workers would be diminished somewhat had the investigators chosen a local standard of comparison, namely, white males for Jefferson County, Kentucky. There would still persist an excess of respiratory cancer deaths, however, but more on the order of 30%. Without having the actual data in hand, we can not state whether this excess would be statistically significant nor can we state the confidence limits within which the true standardized mortality ratio might lie.

In any study of respiratory cancer mortality one must be concerned with the possible effects of important confounding variables (factors that are associated with both the exposure and the outcome under question and which might alternatively account for an observed association). For respiratory cancer a wealth of epidemiologic studies indicates the major potential confounding variables are age and cigarette smoking. The investigators of this study have taken age into account but were unable

to investigate and control for the effects of smoking. Smokers have ten to fifteen times the respiratory cancer mortality of non-smokers, and the observed excess mortality in the cohort might easily be explained if the proportion of smokers exceeded that for the U.S. as a whole. Thus, the observed excess respiratory cancer mortality in this cohort can not be ascribed with certainty to occupational chemical exposures.

The authors of the paper do discuss potential confounding due to socioeconomic status and urban residence and estimate that these factors might account for a 20 - 30% excess in mortality, which is within the range found in their study when one takes residence into account. It seems to us that these effects of socioeconomic might operate primarily through the mechanism of smoking.

We find it intriguing that the respiratory cancer mortality for vinyl chloride monomer (VCM) workers in this plant did not differ from that for all workers in the plant. This finding implies to us, as it did to the authors, that whatever excess risk of respiratory cancer mortality pertained in this plant, is not easily accounted for by vinyl chloride monomer exposure.

The historical cohort analysis does not deal with length of employment or total exposure in this plant. Instead, these factors are examined later in the paper, using a modified case-control approach. Interestingly, 46% of the deaths due to lung cancer among former workers occurred in persons who had worked less than one year at the plant (TABLE 11 of paper). This is a particularly unusual finding for a study in which one

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wishes to ascribe the excess lung cancer deaths to exposures which might have occurred in the plant. Although total chemical exposures were not calculated for workers in this study, it seems likely that most of those who eventually died of lung cancer had fairly low levels of cumulative exposure because they worked in the plant for such a short time. Without additional information we cannot assess whether this pattern of brief periods of work in the plant pertain to all workers or if it is a feature of the lung cancer cases only. The data available to the authors would probably permit one to examine this issue in more detail, using established epidemiologic methods. The results of such a reanalysis could provide more easily interpreted and biologically meaningful information than that presented in the paper.

The other findings of this cohort study, namely, an excess of deaths due to central nervous system cancer and of angiosarcoma of the liver, are not reported in sufficient detail to permit us to make an evaluation. However, the finding of increased risk of angiosarcoma among vinyl chloride workers appears to have been established beyond reasonable doubt in other studies.

PART TWO -- COMPARISON OF LUNG CANCER HISTOLOGY

The second line of inquiry was an investigation into the histology of the lung cancers diagnosed among plant workers. For this study the investigators obtained histologic specimens from 27 of the 45 workers who died of lung cancer. They were unable to obtain specimens among the remaining 40% of the lung cancer deaths. They then selected histologic specimens from a group of patients who were diagnosed in the same hospitals in

which the deceased workers had been diagnosed. In selecting this group of lung cancer patients the investigators attempted to match each worker case with two non-worker lung cancer cases, taking into account age and county of residence. This matching procedure was accomplished with variable success: two-thirds of the community patients met the criteria of age within two years of the worker case while 94% were within six years of age. In four instances only one matched case was obtained. The histological material was reviewed by pathologists who were not aware of the employment status of the individual. These pathologists categorized the tumors using a standard histological classification. Analysis of the differences in the distribution of histological types among the workers compared with the referent patients revealed an excess of only the large cell undifferentiated type, with eight of 27 of the worker-cases having this histology compared to five of 50 of the non-worker-cases (TABLE 6 of paper).

Based on the distribution of histological types and the estimated SMR of 149, the authors estimated the total excess cases of lung cancer by histological type occurring in the cohort of plant workers. Their conclusion from this procedure is that there occurred 3.2 excess deaths due to adenocarcinoma and 10.3 due to large cell undifferentiated carcinoma. They use this information as a basis for their subsequent analyses in the comparison of cumulative chemical exposures among workers, wherein most of their analyses focus on workers who died with adenocarcinoma and large cell undifferentiated carcinoma of the lung.

CRITIQUE

Comparison of the distribution of histologies for cancer cases among workers with the histology distribution among cancer cases in the general population may provide useful information about what types of cancer are truly in excess among workers. For this analysis to be valid the patients from the general population selected as the comparison group must indeed be comparable to the workers with regard to variables other than the exposure of interest. The investigators attempted, with partial success, to control for hospital of diagnosis, county of residence, and age. One factor not taken into account is that the worker lung cancers came only from deceased cases whereas the comparison group were drawn from incident cases. Thus, to the extent that different histological types of lung cancer have differing case fatality rates, those cancers that are rapidly and nearly uniformly fatal will be over-represented in the worker group. In the absence of reliable information on the relative case fatality rates by histology for lung cancer, it is not possible for us to estimate how great this bias might have been. Similarly, there are no reliable data on the relative frequency of occurrence of different histological types of lung cancer by race, age, and sex in the U.S. population or in any other population group, for that matter. This absence of pertinent information also hampers the assessment of the findings in this paper.

One may, however, assess the statistical significance of the findings reported. We tested the distribution of histology among workers and comparison patients depicted in TABLE 6 for statistical significance, and the difference between worker and comparison groups in the frequency of large

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cell undifferentiated carcinoma is not significant at the 5% level (Fisher's exact test, $P = .065$). While the p value approaches the .05 level commonly used, one must take into account that this was the result of one among four possible comparisons. Thus, chance is a plausible explanation for the differences in the distribution of histological types between the two groups. This fact, coupled with the possible biases of selecting cases and comparisons leads us to view with skepticism any inferences based upon these histological differences.

PART THREE -- COMPARISON OF TOTAL EXPOSURES

In this portion of the investigation the authors conducted a comparison of the observed exposures to 19 chemicals among workers deceased with lung cancer with the exposures to these chemicals among a group of workers who had not died of lung cancer. This, in essence, is a case-control study in which the control group is drawn from among the cohort of all workers in the plant. Each deceased lung cancer case was matched to one or more controls based on age and year of first employment in the company. The calculation of exposure for the controls proceeds through a fairly complex series of steps based upon the numbers of days worked in each of many occupations and the exposure score of the occupation. The cumulative dose score of each deceased worker case is calculated and compared to the "expected exposure" based upon the experience of that worker's controls. The differences between observed and expected doses for each worker case are then summed and divided by the number of cases to give a mean (observed minus expected) cumulative dose difference per lung cancer case. The paper presents these figures for all lung cancer cases, for those

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cases that were pathologically reviewed, for cases determined to be due to adenocarcinoma and large cell undifferentiated carcinoma, and for the cases with large cell undifferentiated histological type only. The authors' analyses pertain to 12 of the chemical exposures seen at the plant.

In their paper, the investigators make special note of the excess exposure to PVC dust among lung cancer cases, an excess which is particularly pronounced for the cases with adenocarcinoma and large cell undifferentiated carcinoma. They present these results using statistical significance tests based on a paired sample t-test with a one-tail p-value. Their conclusion based on these analyses is that the PVC dust exposure among all pathologically reviewed lung cancer cases is significantly in excess of that of the controls and that this difference persists when a ten year latency is taken into account. The excess does not achieve statistical significance for all cell types nor for the large cell type alone. It is significant looking at adenocarcinoma and large cell combined, but not when the ten year latency period is taken into account.

CRITIQUE

The method used by these investigators to compare exposures has only recently been reported in a refereed scientific journal and we have been unable to find any other published report of its use. The method does appear to be capable of providing a rough estimate of exposure levels among cases and controls in this sort of case-control within a cohort type of study. However, the exposure scores for various occupations are rank ordered categories and not quantitative measures of exposure. The

authors provide no basis for believing that these ordinal data can be summed and multiplied to produce valid scores of cumulative exposure. One does not know whether the exposure incurred by five days work at level one is equal to one day at level five; in fact, it appears likely that they are not equal. Thus, the estimate of cumulative exposure may not be comparable among individuals and the validity of the estimates is open to doubt.

The analysis and testing of statistical significance for these results raises additional serious questions. The authors of the paper present no basis for use of the paired samples t-test nor do they present any evidence that statistical significance testing of this type is justified with these ordinal data. The "expected" dose estimates are based on data contributed by variable numbers of controls, yet the analysis treats these estimates equally. Also, one control may provide data for several case control comparisons.

It is also not clear how consistent the authors were in assembling the control group. The use of the moving average and the enlargement of the "fellow worker cohort" to include other ages and other years of first work appears to have proceeded fairly arbitrarily. It is not clear what effect these study design issues might have on the validity of the findings.

Inspection of the results provided by the authors on page 12 seems to indicate that there is a deficit of chemical exposure scores for almost all chemicals studied among the lung cancer cases, with the exception of PVC

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dust exposure scores. In fact, and quite surprisingly, exposure scores for vinyl chloride monomer were considerably higher among the controls than in the lung cancer cases. Some of this deficit may be explained by data in TABLE 11. Forty-six percent of all lung cancer deaths were among persons who worked in the plant for less than one year. For the lung cancer deaths with the histology of particular interest to these authors, i.e. adenocarcinoma and large cell undifferentiated, 40% of the workers had been employed for less than one year in the plant and thus had little time to accumulate exposure. The method used by the authors of this study compares those who worked briefly in the plant only to others who worked briefly and those who worked for longer periods to both those who worked for brief and for long periods. The total chemical exposure of the cases and controls in the plant thus is not taken into account.

It is unclear why the investigators chose this type of analysis when they had the option of a cohort analysis. In the cohort analysis, unlike the analysis employed by the investigators, one could take into account total exposure to each chemical and through the use of multivariate techniques one could examine the effect of one chemical exposure while controlling for possible confounding effects of other chemical exposures. One would need, however, to develop more quantitative and biologically meaningful measures of exposure. Again, of course, the important confounding effects of smoking could not be controlled for in this study.

CONCLUSIONS

The report by Waxweiler, et al, on the historical cohort study of lung cancer among workers in a synthetic chemical factor produces reasonably convincing evidence that these workers experienced an excess of mortality due to carcinoma of the respiratory system when compared with the mortality of all U.S. white males. The excess is on the order of one and one-half times, and was statistically significant. The apparent excess of respiratory cancer mortality would have been diminished somewhat had the authors compared these workers to white males for Jefferson County, Kentucky alone. We are unable to determine whether this excess would still be statistically significant. We note, however, that it lies within the range of SMR's (120 to 130) for respiratory cancer that one might encounter as an effect of uncontrolled confounding by cigarette smoking and possibly socioeconomic status. Since with the information available the investigators were unable to control for these variables, one cannot ascribe the elevated SMR's as necessarily due to the effects of employment in the chemical plant. There is, in fact, some reason to doubt that exposures in the plant accounted for much of the excess respiratory cancer mortality, since almost half of the workers who died of these cancers had worked at the plant for less than one year.

The elevated SMR for all plant workers is nearly identical to that noted before by these authors for vinyl chloride monomer workers in this plant. On this basis one may surmise that the previously noted risk for workers with high exposure to VCM is not unique to that group and may be explicable by factors other than their exposure to VCM. However, with the

information available to us in this report, we cannot make any inferences about whether VCM accounts for any or all of the increased risks noted in the total plant cohort, nor can we comment on the potential effects of exposures to other agents. It appears to us that the authors of the study did have available to them sufficient exposure information to permit this type of analysis using the statistical methods traditionally employed in occupational cohort studies. Information from other studies of similarly exposed chemical workers might help in interpreting the validity of the reported findings, but this is beyond the scope of our review.

The comparison of distribution of histologic types of lung cancer among deceased workers with that for a general population group provides little useful information. First, the proportion of lung cancer deaths for which histology was available was small. A number of potential biases may have occurred in constructing both the sample of worker-deaths and the "community" comparison group. Lastly, the results of the histological analyses, while showing some differences in distributions of cell types, did not produce any convincing statistical differences between the two groups. Thus any further analyses based on these observed differences and distributions of histological types rests on a weak foundation indeed.

The analysis of chemical exposure among deceased workers with lung cancer and the comparison workers (termed the serially additive expected dose model analysis) must be viewed with caution. The validity of the model has not been confirmed in any published study and there are reasons to believe that it may not be entirely appropriate for use in the analysis

of the type of data collected in this study. Our major concern has to do with the validity of tests of statistical significance performed on quantal data using this model but we are also concerned about the failure of the model to take into account the effects of total cumulative chemical exposure. Had conventional methods of analysis, such as a cohort approach with quantitative data confirmed the results of this new methodology, our uneasiness might be somewhat allayed. No such information was presented. Consequently, we find the results from the analysis essentially uninterpretable.

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