Breast Cancer Mortality Among PVC Fabricators

Leonard Chiazze, Jr., Sc.D.; Otto Wong, Sc.D.; William E. Nichols, Ph.D.; and Lorraine D. Ference, M.S.

A case-control analysis of breast cancer deaths among PVC fabricators is presented. This study is an extension of a cross-sectional mortality study of deaths occurring among 17 PVC fabricators during the years 1964 to 1973. Relative risk estimates were derived and tested using the Mantel-Haenszel procedure. Although no statistically significant relative risks were found, a least significant relative risk analysis indicated that the underlying relative risk would have to be on the order of three to one in order to be detected. There does seem to be reasonable assurance that very large increases in risk for breast cancer do not exist among these PVC fabricators.

The authors have previously reported the results of a cross-sectional mortality study of deaths occurring among current and former employees of 17 PVC fabricators during the years 1964 to 1973.[1] That study identified 44 deaths among white women for which the underlying cause of death was cancer of the breast. Those 44 deaths attributed to cancer of the breast occurred among employees of eight of the 17 participating companies. On the basis of a proportionate mortality ratio (PMR) analysis, the observed number of deaths from breast cancer was found to exceed the number expected based upon the distribution of deaths by cause and age among all U.S. white women in 1968. The original mortality study focused on deceased employees who worked anywhere in the study plants where PVC fabrication was carried on. A decision was reached to investigate further by carrying out a case-control study which would attempt to determine whether either the cases or controls could have been exposed to PVC during their employment and to estimate the relative risk for breast cancer among those exposed to PVC and those not exposed.

From the Division of Biostatistics and Epidemiology, Georgetown University School of Medicine, Washington, DC 20007 (Dr. Chiazze and Ms. Ference), Tabershaw Occupational Medicine Associates (Dr. Wong), and International Harvester Company (Dr. Nichols, formerly with Organization Resources Counselors, Inc.).

Materials and Methods

Controls were to be selected from among deaths from diseases of the circulatory system (ICDA 390-458, Eighth Revision) and accidents (ICDA E800-E999) since no increased mortality was found for these conditions. An attempt was made to match cases and controls by company (plant, if possible) and age plus or minus five years. Thirty-five of the cases could be matched on both criteria. There were nine breast cancer deaths which could not be matched both on company and age. Controls for these cases were drawn at random from the pool of potential controls with matching on age alone in order that every breast cancer death have at least one matching control. The basis for this report is a total of 44 breast cancer deaths (cases) and 134 controls matched for age and distributed among five companies.

In planning the fieldwork, emphasis was placed on obtaining employment histories on the cases and matched controls. A variety of jobs were held by both cases and controls, ranging from office and clerical work to production jobs such as bench inspector, press operator, trimmer, assembler and sweeper. The wide range of job content and location made it impossible to determine precisely whether there was PVC exposure in every case or the precise length of that exposure. Therefore, a subjective ranking system was developed to classify exposures. Work histories were reviewed with knowledgeable plant personnel, and PVC exposure potential was categorized into five classes — no exposure, improbable exposure, possible exposure, definite exposure, and unknown exposure. The various categories of exposure potential through employment, and examples of each, are as follows:

Classification of Exposure Potential	Examples
No exposure	Employment terminated before PVC use
	PVC processed in a separate building from decedent's work station

	PVC processed in the same building but removed from decedent's work station
Improbable	Decedent handled only fabricated products
Possible	Work station in vicinity of PVC resins; periods of no monitoring or with no detectable level of VCM
Definite	Direct work with PVC resins. Monitoring indicated a detectable level of VCM
Unknown	Employment records not complete enough to determine potential for exposure

Results

A total of 44 breast cancer deaths and 134 controls matched for age and distributed among five companies was available for analysis. Comparison of cases and controls on a variety of variables where information was available, including length of employment with the company, continuous vs. intermittent employment, ever married vs. never married, and child-bearing history, reveals no statistically significant differences ($p > 0.05$) between cases and controls for any of these variables.

The distribution of cases and controls by exposure category is given in Table 1. This classification scheme enabled some definitive exposure statement in 80% of the cases and 92% of the controls.

After matching by age and company, 38 matched sets of cases and controls were developed from the 44 cases and 134 controls. There are fewer matched sets than cases because, in six instances, it was necessary to combine cases of similar age within the same set in order to have at least one control per matched set. The Mantel-Haenszel procedure was used to derive a summary estimate of relative risk and to test for significant departures from unity.[2,3] In this procedure, each of the 38 sets can be viewed as a 2 x 2 contingency table. Thus the i^{th} set can be represented as follows:

	PVC Exposure		
	Yes	No	Total
Cases	A_i	B_i	N_{1i}
Controls	C_i	D_i	N_{2i}
Total	M_{1i}	M_{2i}	T_i

Relative risk is defined as the ratio of the probability of dying from cancer of the breast among women exposed to PVC to the probability for women not exposed. Estimates of these individual probabilities are not available from a case-control study. However, a measure of estimated relative risk from case control studies as suggested by Mantel and Haenszel has been calculated as:

$$R = \frac{\sum_i \frac{A_i D_i}{T_i}}{\sum_i \frac{B_i C_i}{T_i}}$$

To assess whether the departure from unity of an observed relative risk is too great to have occurred by chance alone, a summary chi-square test corrected for continuity was performed using the Mantel-Haenszel procedure. The calculated chi-square must be 3.84 or larger in order to conclude with 95% assurance that the observed relative risk did not differ from unity by chance alone.

Combining the five exposure categories into two may be accomplished in a variety of ways resulting in several possible relative risk measures. For example:

1. Yes = Definite exposure only
   No = No exposure only
   (Ignore improbable, possible, unknown)
   $R = 1.81$ $\chi^2_{MH} = 0.0189$ (not significant)
2. Yes = Definite + improbable + possible + unknown
   No = No
   $R = 1.94$ $\chi^2_{MH} = 1.119$ (not significant)
3. Yes = Definite + possible
   No = No + improbable
   (Ignore unknowns)
   $R = 0.624$ $\chi^2_{MH} = 0.0194$ (not significant)
4. Yes = Definite + possible + unknown
   No = No + improbable
   $R = 2.73$ $\chi^2_{MH} = 1.548$ (not significant)

None of the above calculated relative risks, including number 2, which treats anything other than no exposure as definitely exposed, are statistically significant; i.e., they may have occurred by chance alone. Similar analyses were carried out on a company-by-company basis. None of the relative risks so calculated is significantly different from unity.

Conclusions

The results presented here must be interpreted with caution. Absence of a statistically significant relative risk does not demonstrate that there is not an excess risk of death from breast cancer among white women employees with PVC exposure. In fact, when no statistically significant relative risks are found, it is pertinent to ask what the chances are of detecting an increase of a given magnitude from the available data. Using the method described by Walter,[4] the authors have subjected each of

Table 1. — Distribution of 44 Breast Cancer Deaths and 134 Matched Controls by Exposure Category.

Exposure Category	Cases		Cases	
	No.	%	No.	%
No exposure	27	61.4	97	72.4
Improbable exposure	6	13.6	17	12.6
Possible exposure	0	0	4	3.0
Definite exposure	2	4.5	6	4.5
Unknown exposure	9	20.5	10	7.5
Total	44	100	134	100

the relative risk estimates to a least significant relative risk analysis under the conditions that they desired 95% assurance that a risk of such magnitude, if observed, did not occur by chance alone and 80% probability of detecting the least significant relative risk if it exists. Results of that analysis are as follows:

1. Definite exposure only vs. no exposure only
   Relative risk estimate = 1.81
   Least significant relative risk = 6.77
2. Definite + improbable + possible + unknown vs. no exposure
   Relative risk estimate = 1.94
   Least significant relative risk = 2.92
3. Definite + possible vs. no exposure + improbable
   Relative risk estimate = 0.624
   Least significant relative risk = 5.02
4. Definite + possible + unknown vs. no exposure + improbable
   Relative risk estimate = 2.73
   Least significant relative risk = 3.41

Even in case number 2, where all but "no exposure" are counted as exposed, the smallest relative risk which could be detected from these data is nearly 3:1. In this instance, over 130 cases and 130 controls would have been necessary to detect a true doubling of the risk under the specified conditions. In order to achieve 95% probability of detecting a true two-fold risk, if it in fact existed, well over 200 cases and 200 controls would have been required. Given the sample size in this study and the percentage of controls exposed (a percentage which was unknown at the start of the study), it would be possible to detect only very large increases in risk. There seems reasonable assurance, therefore, that such very large increases in the risk for breast cancer do not exist among these PVC fabricators.

References

1. Chiazze L, Nichols WE, and Wong O: Mortality among employees of PVC fabricators. *J Occup Med* 19:623-628, 1977.
2. Mantel N and Haenszel W: Statistical aspects of the analysis of data from retrospective studies of diseases. *J Natl Cancer Inst* 22:719-748, 1959.
3. Pike MD and Morrow RH: Statistical analysis of patient-control studies in epidemiology: Factor under investigation an all-or-none variable. *Br J Prev Soc Med* 24:42-44, 1970.
4. Walter SD: Determination of significant relative risks and optimal sampling procedures in prospective and retrospective comparative studies of various sizes. *Am J Epidemiol* 105:387-397, 1977.

Light in Darkness

I am not tragic or desponding by nature. Temperamentally I am buoyant and hopeful. Through the darkness I always see a light — a bright star that no misfortune ever quite hides from me. . .

With an embossed book on my knee, or seated at my typewriter, I am not conscious of any handicap. In spirit and mind I am untrammelled. Imagination rides Olympian horses. Once my foot is in the stirrup, I am off to the uttermost isles of thought. I ought to say also that I have received the most wonderful kindness from my fellow creatures. Everyone has given me of his best in proportion to the richness of his nature and the goodness of his heart.

— Helen Keller, as quoted in *Helen and Teacher* by Joseph P. Lash. Published by Delacorte Press, New York, N.Y.