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Mortality Among PVC-Fabricating Employees

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The results of a cross-sectional mortality study of 3847 deaths occurring among current and former (white) employees of 17 PVC fabricators during 1964-1973 are presented. Sex-race-cause-specific proportionate mortality ratios (PMR's) were computed by using two separate standards: one, the U.S. mortality in 1968; the second, U.S. mortality for the individual years 1964-1973. In addition, a case-control analysis, based upon 44 breast cancer deaths among white female employees, is presented. PMR's are significantly different from unity for all cancers, and for cancers of the digestive system among both white males and white females. Although observed deaths significantly exceeded expectations for cancer of the breast, a subsequent case-control analysis reveals no statistically significant relative risks for breast cancer.

Introduction

In March, 1974, Organization Resources Counselors (ORC) was requested by representatives of PVC producers who are members of ORC's Occupational Safety and Health Standards Group, to carry out a study of health risks to employees working in the PVC fabricating industry. After considering a number of alternative study designs, it was decided that a cross-sectional mortality study would best meet the need for providing information as rapidly as possible. Details regarding reasons for selecting this type of study, the actual study design and results of the inquiry have been reported previously (*1*).

In the original report, proportionate mortality ratios were calculated according to the method of Guralnick (*2*) and by using the sex-cause-age specific distribution of deaths among U.S. whites in 1968 as the basis for determining expectation (*3*). For the current report, we have analyzed the data using the Mantel-Haenszel procedure both for determination of PMR's and in order to test whether PMR's differ significantly from unity (*4*, *5*). In addition, PMR's are presented using two separate standards as the basis for expectation.

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A follow-up to the cross-sectional mortality investigation, utilizing deaths among white women for whom the underlying cause of death was cancer of the breast, was undertaken (*6*), and results of the case-control analysis will be presented.

Materials and Methods

Although alternative study designs were considered, several factors led to the decision to carry out a cross-sectional mortality study. First, the primary study objective was to determine relatively quickly whether any angiosarcoma deaths could be identified among the study group and this was best accomplished by examining causes of death among relatively recent decedents. Second, it would not have been possible to identify clearly and completely (if at all) the cohort of workers necessary for a historical cohort mortality study within a reasonably short period of time. As a result, the study was based upon 4336 deaths which occurred during the years 1964-1973 among active or retired employees of 17 companies engaged in PVC fabrication (Table 1). This report will be restricted to the 3847 deaths among whites, since the number of deaths for most causes among nonwhites was quite small, making interpretation of cause specific mortality difficult at best.

Since the population at risk could not be deter-

Table 1. Distribution of deaths among employees of 17 PVC fabricators by race and sex, 1964–1973.

Race	Total	Sex		
		Male	Female	Unknown
Total	4336	3676	658	2
White	3847	3252	595	0
Nonwhite	198	174	24	0
Unknown	291	251	39	2

mined, mortality rates as measures of risk could not be calculated. Rather, results are summarized in terms of proportionate mortality ratios (PMR) calculated according to the method of Mantel-Haenszel (*5*). Two separate standards have been employed. The first is the sex-cause-age specific distribution of deaths among U.S. whites in 1968 (1968 Standard). A second standard employs the sex-cause-age specific distribution of deaths among U.S. whites in each of the years 1964-1973 (1964-1973 standard). Cause-specific PMR's based upon the 1968 standard are adjusted for age, race and sex. Cause-specific PMR's based upon the 1964-1973 standard are adjusted for year of death as well as for age, race and sex.

The Mantel-Haenszel procedure for assessing the statistical significance of a difference between the observed and expected numbers of deaths for a specific cause requires the construction of a series of 2×2 contingency tables as shown in Table 2. Separate tables are constructed for each level of the factor(s) to be adjusted for. If, for example, we wish to compute a PMR for all decedents for cause X, adjusted for age (five age groups) and year of death (10 years: 1964-1973), i.e., 1964-1973 standard, we would have 50 2×2 tables: age < 35, year of death 1964; age < 35, year of death 1965; . . . ; age < 65, year of death 1973. Observed deaths and expected deaths are summed over the 50 separate 2×2 tables to produce a PMR for cause X, adjusted for age and year of death. The resulting age-year of death-adjusted PMR compares the number of deaths from cause X observed in the study group to the number of deaths from cause X expected in the study group, if the proportion of total deaths ascribed to cause X was the same, age group by age group and year by year, as for the comparison group.

Table 2. Construction of 2×2 contingency tables.

	Number of deaths in group I, attributed to		Total deaths
	Specified cause	Other causes	
Study group	A_i	C_i	N_{1i}
Standard	B_i	D_i	N_{2i}
Total	M_{1i}	M_{2i}	T_i

The statistical significance of the PMR (a test of the hypothesis that the PMR is 1.0 against the alternative that the PMR is different from 1.0) is evaluated by using the Mantel-Haenszel continuity corrected chi-square with one degree of freedom, i.e.,

$$\chi_{MH}^2 = \frac{(|\Sigma A_i - \Sigma E(A_i)| - \frac{1}{2})^2}{\Sigma \ \mathrm{Var}\ A_i} \qquad (1)$$

where

$$\mathrm{Var}\ A_i = \frac{N_{1i}N_{2i}M_{1i}M_{2i}}{T^2_i(T_i - 1)}$$

$$E(A_i) = \text{Expected value of } A_i = (M_{1i}\,N_{1i})/\,T_i$$

The case-control analysis is based on 44 deaths among white females in the study with cancer of the breast as the underlying cause of death. Controls were drawn from deaths due to diseases of the circulatory system and accidents, and matched by age plus or minus five years and company, if possible. Forty of the cases were matched on both criteria and four on the basis of age alone. The basis for the case-control analysis, then, is the 44 breast cancer deaths and 134 matched controls distributed among eight of the 17 companies.

Results

Proportionate Mortality Ratios

Cause specific PMR's adjusted for age are presented for white male and white female employees in Tables 3 and 4. For Table 3, expected numbers of deaths are based on the cause-sex-age specific distribution of deaths among U.S. whites applied to the study group. For Table 4, PMR's are adjusted for year of death as well as race, sex and age. Statistically significant departures from unity (i.e., PMR = 1) are evaluated by using the Mantel-Haenszel continuity corrected chi-square with one degree of freedom. Causes of death for which the calculated chi-square indicated a statistically significant excess or deficit at the $\alpha = 0.05$ level of significance are indicated in the table. It is important to remember that when carrying out a large number of significance tests, some number will turn out to be significant on the basis of chance alone. When dealing with a large number of tests for PMR's, it may be more appropriate to consider the Mantel-Haenszel test as a screening device rather

than giving it a strict probabilistic interpretation.

With these caveats, we see that based upon the 1968 standard, among white males there are statistically significant PMR's for all cancers, digestive cancer, respiratory cancer and other and unspecified cancers (Table 3). Among white females, PMR's are significantly different from one for all cancers, digestive cancers, breast cancer, urinary cancer and other and unspecified cancers. In contrast to white males, the PMR for urinary cancer among white

Table 3. Observed deaths and cause specific proportionate mortality ratios (PMR) for employees of 17 PVC fabricators by sex (white only), 1964–1973 (expectations based on U.S. mortality, 1968).

		Male		Female	
Cause of death	ICDA 8th Revision	Observed deaths	PMR	Observed deaths	PMR
All causes	000–999	3252	1.0000	595	1.0000
All cancer	140–209	670	1.1905[a]	181	1.3266[a]
Buccal cavity and pharynx	140–149	15	0.8382	3	—
Digestive organs and peritoneum	150–159	212	1.3058[a]	53	1.5134[a]
Stomach	151	41	1.3000	8	1.6226
Large intestine	153	72	1.3688[a]	24	1.5785[a]
Rectum	154	26	1.3230	8	2.0822
Liver	155	6	1.4306	0	—
Pancreas	157	37	1.1307	7	1.1612
Other and unspecified digestive	152, 156, 158, 159	30	1.3861	6	1.3680
Respiratory system	160–163	206	1.1647[a]	12	1.0119
Larynx	161	9	1.0695	0	—
Trachea, bronchus and lung	162	194	1.1704[a]	12	1.0788
Other	160, 163	3	—	0	—
Breast	174	0	—	44	1.3710[a]
Female genital organs	180–184	—	—	19	0.8232
Cervix	180	—	—	5	0.6827
Corpus	181, 182	—	—	6	1.2911
Ovary	183	—	—	7	0.6714
Other	184	—	—	1	—
Male genital organs	185–187	42	0.7936	—	—
Prostate	185	41	0.8223	—	—
Other	186, 187	1	—	—	—
Urinary organs	188–189	37	1.1153	11	2.9296[a]
Bladder	188	20	1.0053	4	—
Kidney	189	17	1.2800	7	3.4535[a]
Brain and nervous system	191–192	16	1.1499	4	—
Lymphomas	200–203, 208, 209	44	1.3560	9	1.1900
Leukemias	204–207	19	0.8117	1	—
Other and unspecified cancers	170–173, 190, 193–199	79	1.6132[a]	25	1.9584[a]
Other causes					
Diabetes	250	43	0.8655	10	0.6540
Diseases of circulatory system	390–458	1930	1.0516[a]	278	0.9087[a]
Heart disease	(390–398), 402, 404, (410–429)	1495	1.0625[a]	188	0.9009
Rheumatic heart disease	393–398	16	0.6373	7	0.7502
Hypertensive disease	400–404	36	1.0575	3	—
Ischemic heart disease	410–413	1381	1.0599[a]	158	0.8644[a]
Myocardial infarction	410	898	1.1040[a]	93	0.9888
Cerebrovascular disease	430–438	290	0.9913	65	0.9133
Other circulatory	450–458	40	1.5294[a]	8	1.2398
Diseases of respiratory system	460–519	144	0.6344[a]	17	0.5804[a]
Cirrhosis of liver	571	42	0.6675[a]	3	—
Cholelithiasis, cholecystitis and cholangitis	574–575	7	1.1018	3	—
Accidents, poisonings and violence	800–999	187	0.7007[a]	46	1.1364
Accidents	800–949	134	0.7043[a]	37	1.3369
Suicide	950–959	39	0.7427	2	—
All other causes	Residual	229	1.0410	57	1.1500

[a]PMR significantly different from one at $\alpha = 0.05$.

females is high and, although based upon only 11 deaths, is statistically significant. On the other hand, in contrast to the observation in white men, the PMR for respiratory cancer among white women is very close to unity. Similar to the observation in white men, mortality from cirrhosis of the liver is low, but the corresponding number of observed deaths is quite small.

Among both white male and female employees, diseases of the circulatory system account for a large percentage of total deaths. In each case, observed numbers of deaths are close to expected,

Table 4. Observed deaths and cause specific proportionate mortality ratios (PMR) for employees of 17 PVC fabricators by sex (white only), 1964–1973 (expectations based on U.S. mortality, 1964–1973).

		Male		Female	
Cause of death	ICDA 8th Revision	Observed deaths	PMR	Observed deaths	PMR
All causes	000–999	3252	1.0000	595	1.0000
All cancer	140–209	670	1.1567[a]	181	1.2956[a]
Buccal cavity and pharynx	140–149	15	0.8340	3	—
Digestive organs and peritoneum	150–159	212	1.2667[a]	53	1.4813[a]
Stomach	151	41	1.3084	8	1.6541
Large intestine	153	72	1.3239[a]	24	1.5490[a]
Rectum	154	26	1.3164	8	2.1165
Liver	155	6	0.9801	0	—
Pancreas	157	37	1.1202	7	1.1461
Other and unspecified digestive	152, 156, 158, 159	30	1.3139	6	1.4548
Respiratory system	160–163	206	1.1155	12	0.9100
Larynx	161	9	1.0563	0	—
Trachea, bronchus and lung	162	194	1.1266	12	0.9787
Other	160, 163	3	—	0	—
Breast	174	0	—	44	1.3448[a]
Female genital organs	180–184	—	—	19	0.8161
Cervix	180	—	—	5	0.6869
Corpus	181, 182	—	—	6	1.2738
Ovary	183	—	—	7	0.6597
Other	184	—	—	1	—
Male genital organs	185–187	42	0.7687	—	—
Prostate	185	41	0.7964	—	—
Other	186, 187	1	—	—	—
Urinary organs	188–189	37	1.0942	11	2.8365[a]
Bladder	188	20	0.9884	4	—
Kidney	189	17	1.2517	7	3.4206[a]
Brain and nervous system	191–192	16	1.1267	4	—
Lymphomas	200–203, 208, 209	44	1.3525	9	1.1944
Leukemias	204–207	19	0.8019	1	—
Other and unspecified cancers	170–173, 190, 193–199	79	1.5975[a]	25	1.9564[a]
Other causes					
Diabetes	250	43	0.8993	10	0.6743
Diseases of circulatory system	390–458	1930	1.0538[a]	278	0.9132[a]
Heart disease	(390–398), 402, 404, (410–429)	1495	1.0600[a]	188	0.9035
Rheumatic heart disease	393–398	16	0.7030	7	0.8009
Hypertensive disease	400–404	36	1.1541	3	—
Ischemic heart disease	410–413	1381	1.0512[a]	158	0.8522[a]
Myocardial infarction	410	898	1.1148[a]	93	0.9962
Cerebrovascular disease	430–438	290	1.0011	65	0.9184
Other circulatory	450–458	40	1.5062[a]	8	1.2256
Diseases of respiratory system	460–519	144	0.6883[a]	17	0.6546
Cirrhosis of liver	571	42	0.6438[a]	3	—
Cholelithiasis, cholecystitis and cholangitis	574–575	7	1.1536	3	—
Accidents, poisonings and violence	800–999	187	0.6991[a]	46	1.1173
Accidents	800–949	134	0.7084[a]	37	1.3266
Suicide	950–959	39	0.7034[a]	2	—
All other causes	Residual	229	1.0246	57	1.1197

[a]PMR significantly different from one at $\alpha = 0.05$.

Table 5. Distribution of 44 breast cancer deaths and 134 matched controls by exposure category.

Exposure category	Breast cancer, cases		Matched control	
	Number	%	Number	%
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
	44	100	134	100

although statistically significant.

Results based upon the 1964-1973 standard are, in general, consistent with those on the 1968 standard (Table 4). There are, however, some notable exceptions. In general, the PMR's based upon the 1964-1973 standard are lower than those based upon the 1968 standard. Further, the PMR for respiratory cancer among white males is not significantly different from one when based on the 1964-1973 standard. Among white women, the PMR for other (noncancer) respiratory deaths is significantly below unity based on the 1964-1973 standard.

Case-Control Analysis

Comparison of cases and controls on a variety of variables where information was available, including length of employment, ever married versus never married, and child-bearing history, reveals no statistically significant differences ($p > 0.05$) between cases and controls for any of these variables.

Review of employment histories for cases and controls revealed a wide variety of jobs 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 plant personnel and PVC exposure potential was categorized into five classes—no exposure, improbable exposure, possible exposure, definite exposure and unknown exposure. This classification scheme enabled some definitive exposure statement in 80% of the cases and 92% of the controls (Table 5).

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 (*4*, *7*). In this procedure, each of the 38 sets can be viewed as a 2×2 contingency table. Thus, the ith set can be represented as in Table 6.

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 in Eq. (2). 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.

$$R = \Sigma_i (A_i D_i T_i)/\Sigma_i (B_i C_i / T_i) \qquad (2)$$

Combining the five exposure categories into two may be accomplished in a variety of ways, resulting in several possible relative risk measures as shown in Table 7.

None of the calculated relative risks, including the second shown which treats anything other than no exposure as definitely exposed, are statistically

Table 6. Representation of ith set.

	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

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.

Discussion and Summary

The cross-sectional mortality study was designed with two objectives. The first was to determine if any angiosarcoma deaths had occurred among employees of the PVC fabricators under study. Since no angiosarcoma deaths were found among the employees studied, the first question has an unequivocal answer. A secondary objective was that of examining the distribution of deaths by cause among the employees under study. Implicit in that objective is the question of whether or not that distribution is, in some sense, unusual. There is no unequivocal answer to the latter question. Whether or not an observed distribution of causes of death is unusual clearly relates to the standard or comparison population as well as the analytic methodology (*8*). This is illustrated by the observation that there are PMR's which are significantly different from unity on the 1968 standard and not on the 1964-1973 standard. However, it seems much more important to focus on the large area of agreement between the two standards rather than on the few areas of disagreement.

On the basis of the PMR analyses, there are statistically significant excesses in total cancer mortality among both white males and white females when compared to the distribution of deaths for the total United States specific for color and sex and adjusted for age. Excesses in cancer mortality appear concentrated in cancers of the digestive system and, in particular, in cancers of the intestine for both men and women. In addition, there is a suggestion that mortality from cancer of the breast and urinary organs among white women employees is higher than that for the total U.S. There are, however, several reasons why definitive interpretation is difficult. Factors meant to suggest that proportionate mortality analyses must be interpreted cautiously have been reviewed previously (*9-13*). However, while these results must be interpreted with caution, they appear to be consistent with previously studied workers and suggest the need for some continuing investigation (*1*).

One such follow-up investigation has been presented here in the form of a case-control study involving the 44 breast cancer deaths. On the basis of a case-control analysis, estimates of relative risk were derived but none of these relative risk estimates is significantly different from one, although such results 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 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 (*14*), we have subjected each of the relative risk estimates (Table 7) to a least significant relative risk analysis under the conditions that we desire 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.

Even in the case where all but no exposure are counted as exposed, the smallest relative risk which could be detected from these data is nearly 3:1. Nearly 200 cases and 200 controls would have been necessary to detect a true doubling of the risk under the specified conditions. Given the sample size in this study and the percentage of controls exposed (a percentage which was unknown at the

Table 7. Relative risk (RR) and least significant relative risk (LSRR) estimated for contrasts of various exposure category combinations.

Contrast	Number of cases	RR (Relative risk) estimate[a]	LSRR (Least significant relative risk) estimate[b]
Definite exposure vs. no exposure	29	1.81	6.77
Definite + improbable + possible + unknown exposure vs. no exposure	44	1.94	2.92
Definite + possible exposure vs. no + improbable exposure	35	0.624	5.02
Definite + possible + unknown exposure vs. no + improbable exposure	44	2.73	3.41

[a]None of the relative risk estimates are statistically significantly different from unity ($p > 0.05$).
[b]The true relative risk would have to be at least this large to have an 80% assurance of detection (i.e., power = 0.80) with a type I error of 0.05 (i.e., $\alpha = 0.05$).

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, but no such statement can be made for possibly smaller increases in risk.

REFERENCES

1. Chiazze, L., Jr., Nichols, W. E., and Wong, O. Mortality among employees of PVC fabricators. J. Occup. Med. 19: 623-628 (1977).
2. Guralnick, L. Mortality by Occupation and Cause of Death Among Men 20-64 Years of Age: United States, 1950 (Vital Statistics-Special Reports, Vol. 53, No. 3). U.S. Govt. Printing Office, Washington, D.C., 1963.
3. National Center for Health Statistics. Vital Statistics of the United States, 1968, Volume II, Mortality, Part A. Washington, D.C., U.S. Govt. Printing Office, 1972, pp. 140-205.
4. Mantel, N. and Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22: 719-748 (1959).
5. Li, F. P., Fraumeni, J. F., Jr., Mantel, N., and Miller, R. W. Cancer mortality among chemists. J. Natl. Cancer Inst. 43: 1159-1164 (1969).
6. Chiazze, L., Jr., Wong, O., Nichols, W. E., and Ference, L. Breast cancer mortality among PVC fabricators, J. Occup. Med. 22: 677-679 (1980).
7. Pike, M. D., and Morrow, R. H. Statistical analysis of patient-control studies in epidemiology: factor under investigation an all-or-none variable. Brit. J. Prev. Soc. Med. 24: 42-44 (1970).
8. Chiazze, L., Jr. Problems of study design and interpretation of industrial mortality experience. J. Occup. Med. 18: 169-170 (1976).
9. Redmond, C. K., and Breslin, P. P. Comparison of methods for assessing occupational hazards. J. Occup. Med. 17: 313-317 (1975).
10. Monson, R. R., Peters, J. M., and Johnson, M. N. Proportional mortality among vinyl-chloride workers. Lancet ii: 397-398 (1974).
11. Lloyd, J. W., and Ciocco, A. Long term mortality study of steelworkers: I. Methodology. J. Occup. Med. 11: 299-310 (1969).
12. Redmond, C. K., Ciocco, A., Lloyd, J. W., and Rush, H. W. Long term mortality study of steelworkers: IV. Mortality from malignant neoplasms among coke oven workers. J. Occup. Med. 14: 621-629 (1972).
13. Tabershaw, I. R., and Gaffey, W. R. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J. Occup. Med. 16: 509-518 (1974).
14. Walter, S. D. 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).