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PLAINTIFF'S EXHIBIT WRG-752

CAMBRIDGE

TO: V. Bakeman/New York
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DATE: 28 July 1982

FROM: H. A. Eschenbach

SUBJECT: Mortality Study -- Richard Monson

Attached is a copy of the "quick-and-dirty" mortality study done by Richard Monson at the Harvard School of Public Health. Apparently, he completed it rather quickly after our meeting but sat on it while he went on a trip to China.

As you will observe in Table 1, our major problem is death from respiratory cancer. This is no surprise. There are no other statistically significant aberrations from norms.

While we cannot say for certain that our collection of death certificates is complete or representative, there is no reason to believe that there is any bias in our accumulation of them. Therefore, one must assume that NIOSH's study will be in the same range. NIOSH would possibly not pursue the mortality portion of their study if we provided this information to them. On the other hand, I see no advantage or disadvantage in doing so.

Harry Eschenbach

HAE/cs

attachment

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Cause of Death Among
Sixty-six Libby Employees

Richard R. Monson, M.D., Sc.D.

4/5/82

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This is an analysis of 66 death certificates for Libby employees of W.R. Grace & Company.

METHOD

The 66 deaths occurred between 1950 and 1981, inclusive. The deaths were coded according to the 8th revision, International Classification of Diseases. The observed deaths were distributed by age at death and year of death in five-year strata. Expected deaths were computed using the USDR computer program (1). Expected numbers were based on age-time-cause specific proportional mortality ratios for U.S. white males.

RESULTS

As seen in Table 1, there was an excess of cancer of the respiratory system - 14 observed and 5.0 expected. Two of these cancers were mesotheliomas. There was only a small excess of death from non-malignant respiratory disease. As seen in Table 2, most of the excess being cancer has occurred since 1975.

COMMENT

The data in this report are consistent with excess death due to respiratory cancer as a result of exposure to asbestos.

REFERENCE

1. Monson RR: Analysis of relative survival and proportional mortality. Computers and Biomedical Research 7: 325-332, 1974.

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Table [illegible]. Cause of death among [illegible]

ICD No.[a]	Cause of Death	Observed	Expected[b]	Obs/Exp
-	All	66	66.0	1.0
140-209	All cancer	20	14.0	1.4
150-159	Digestive	3	3.9	0.8
160-164	Respiratory[c]	14	5.0	2.8[d]
185-189	Genitourinary[e]	3	1.8	1.7
-	Residual	0	3.3	-
390-458	Circulatory	28	35.5	0.8
460-519	Respiratory	5	4.3	1.2
800-999	External causes	4	4.7	0.9
-	Residual	9	7.5	-

a. International Classification of Diseases, Eighth Revision.

b. Expected numbers computed on the basis of age-time-cause specific proportional mortality ratios for U.S. white males.

c. Lung cancer - 11, mesothelioma - 2, mediastinal cancer - 1.

d. 95% confidence interval = 1.7 - 4.5.

e. Prostate cancer - 3.

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Table 2. Observed and expected number of respiratory cancer according to year of death

Year	Observed	Expected
< 1965	0	0.5
1965-69	3	0.8
1970-74	1	1.1
1975-79	7	1.8
≥ 1980	3	0.8
	14	5.0

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[illegible] 7, 325–332 (1974)

Analysis of Relative Survival and Proportional Mortality*

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A computer program utilizing cause-age-time-sex-race-specific mortality or incidence rates is described. The program is used to determine the expected number of deaths or cases of disease in a cohort. Also, among a group of persons known to be dead, the number expected to have died of each cause can be calculated using proportional mortalities. Mortality rates based on United States vital statistics have been assembled for 57 causes of death for white males, white females and non-white males for each five-year age and time period from 1925 through 1969. Proportional mortalities and proportional cancer mortalities have been calculated. Incidence rates from the Connecticut Cancer Registry are available. The computer program is general and can be modified to use other sets of rates in determining the expected number of deaths in any study population.

Two dissimilar epidemiologic techniques, the estimation of relative survival and proportional mortality, share a common ground: each is dependent upon a standard set of deaths. In relative survival, standard death rates are calculated and are used to compute the expected number of total deaths in a cohort. In proportional mortality the number of deaths due to a specific cause is divided by the number of total deaths and this proportion is used to compute the expected number of cause-specific deaths among a group of deceased persons.

This paper describes a computer program developed to analyze cohort studies using relative survival and its analogues and to analyze studies using proportional mortality. These techniques have been fully described and illustrated by other authors (1–3). The standard death rates and proportional mortalities are based on cause-age-time-sex-race-specific data for the population of the United States from 1925 to 1967.

CALCULATION OF STANDARD RATES

[illegible] population. For each year from 1925 to 1967, the enumerated or [illegible] race-specific population of the United States death registration area was

* Supported [illegible] program-project [illegible] from the National Cancer Institute and [illegible] from the National Institute of Environmental Health Sciences.

abstracted (4, 5). For the years 1925–34, the population was grouped in 10-year age groups (0–4, 5–14, . . ., 85+). For succeeding years, the population was grouped in five-year age groups (0–4, 5–9, . . ., 85+). For each age group, the average population during each five year period (1925–29, 1930–34, . . ., 1965–67) was calculated for white males, white females and non-white males.

Standard deaths. For each year from 1925 to 1967, the numbers of persons dying from selected causes of death were abstracted from United States Vital Statistics (5), specific for age, sex and race. To date, information on 23 categories of cancer and 34 categories of other causes have been abstracted. Prior to 1933 the data are derived from the states included in the death registration area. The age-time breakdown corresponds to that for the standard population. The average number of age-specific deaths per year within each five-year time period was calculated. For each cause a cause-of-death code was assigned according to the Seventh Revision of the International Classification of Diseases (6). Since codes and coding procedures change with time, causes from different times were grouped according to title of cause of death rather than according to ICD code.

Standard rates. For each age-time period for each race and sex the number of deaths per 1000 population per year was calculated. For some five-year periods the

TABLE 1

MORTALITY RATES FOR ALL CAUSES FOR WHITE FEMALES IN UNITED STATES ACCORDING TO AGE AND YEAR OF DEATH, EXPRESSED AS NUMBERS OF DEATHS PER 1000 POPULATION PER YEAR

Age at death	Year of death								
	1925–	1930–	1935–	1940–	1945–	1950–	1955–	1960–	1965–
0–	15.9	13.0	12.1	9.7	7.4	5.6	5.0	4.4	3.8
5–	1.6	1.3	1.2	0.8	0.6	0.5	0.4	0.4	0.3
10–	1.6	1.3	1.0	0.7	0.5	0.4	0.3	0.3	0.3
15	2.9	2.1	1.5	1.0	0.9	0.6	0.5	0.5	0.5
20–	2.9	2.1	2.1	1.5	1.1	0.7	0.6	0.6	0.6
25–	4.0	3.2	2.6	1.7	1.3	0.9	0.7	0.7	0.7
30–	4.0	3.2	3.0	2.2	1.6	1.2	1.0	1.0	1.0
35–	5.8	4.8	3.7	2.9	2.3	1.7	1.5	1.5	1.5
40–	5.8	4.8	5.0	3.9	3.2	2.7	2.4	2.3	2.4
45–	10.1	9.0	7.0	5.7	4.8	4.1	3.7	3.6	3.7
50–	10.1	9.0	9.9	8.6	7.4	6.4	5.7	5.5	5.6
55–	21.0	19.6	14.7	12.9	11.0	9.7	8.1	8.1	8.3
60–	21.0	19.6	22.4	19.6	17.2	15.2	13.7	12.5	12.4
65–	49.2	45.4	34.9	30.7	26.7	24.2	22.6	20.9	22.5
70–	49.2	45.4	54.2	51.1	45.3	40.4	36.6	34.0	33.4
75–	118.2	107.9	92.5	81.2	74.6	66.8	62.6	57.3	55.0
80–	118.2	107.9	141.7	131.9	114.3	109.0	105.4	100.4	94.4
85+	281.1	244.7	227.2	220.5	208.9	191.4	196.0	195.8	200.6

numbers of deaths for certain causes are not published; the rates during these periods are assumed to be those of preceding or succeeding periods. The rates for 1965-69 are based on deaths from 1965-67 only. As an example, total death rates for all causes for white females are presented in Table 1. (The rates have been truncated for purposes of presentation.)

Proportional mortalities. The denominator of a proportional mortality is the number of deaths due to all causes. The numerator is the number of deaths due to a specific cause. The proportional mortalities for each cause were calculated, according to the age-time distribution presented in Table 1.

Proportional cancer mortality. The denominator of a proportional cancer mortality is the number of deaths due to cancer. The numerator is the number of deaths due to a specific cancer. Proportional cancer mortalities were calculated for each cancer, according to the age-time distribution presented in Table 1.

Data Analysis Using Relative Survival

For each member of the study cohort, the following information is needed: sex, race, age at entry, year of entry, years of survival, status at end of study (live, deceased or lost to follow-up) and cause of death, where appropriate.

The steps in the computer program are described below. Except for step 8, each table has the format of Table 2. The data may or may not be calculated, depending upon the program option selected. Also, options are available as to the number of tables to be printed.

Step 1. The death rate matrix is read.

Step 2. The age-year-of-entry distribution of the study cohort is determined in five-year groupings.

Step 3. The age-time-specific person-years of the study cohort are calculated. A person is assumed to have entered on July 1 of the year of entry and at the midpoint of the age of entry. If a person is lost to follow-up, withdrawal is assumed to have occurred on July 1 of the year of withdrawal. (Options are available to consider lost persons to have died at the time of loss or to be alive until the common closing data of the study.) A person entering and leaving in the same year contributes 0.25 person-years. A person who is a live withdrawal is withdrawn at the common closing date, usually January 1 or July 1. As an example, consider the person described by Hill (7). He entered the study in 1952 at age 23 and left in 1962. His person-years of survival would be distributed as shown in Fig. 1. The method used in this program is less precise for an individual than Hill's method, since the exact days of survival are not computed. For the total population, however, essentially no error should be introduced, since persons who are given too many partial years of survival are counterbalanced by those with too few.

The total person-years in a study of survival following carcinoma of the endometrium (8) are distributed as illustrated in Table 2.

Step 4. The age-time distribution of the observed deaths is determined. The observed rates are calculated by dividing the observed deaths by the person-years of survival.

Step 5. The age-time-specific expected deaths are calculated by multiplying the age-time-specific standard death rates by the age-time-specific person-years of follow-up.

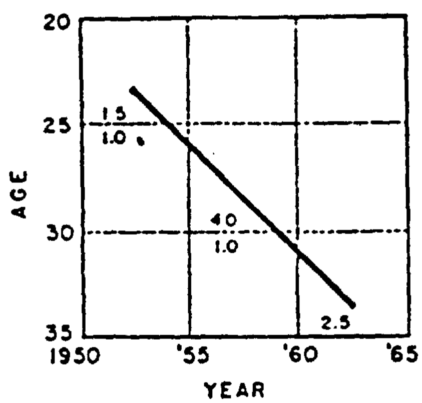

FIG. 1. Person-years experienced by a person entering at age 23 in 1952 and leaving in 1962.

Step 6. Mortality ratios are calculated by dividing each observed number of deaths by each expected number of deaths.

Step 7. The probability that the observed number of deaths differs significantly from the expected numbers of deaths is calculated using a modification of the Mantel-Haenszel procedure (9). A Mantel-Haenszel X^2 is calculated for each marginal ratio as well as for the total observed/expected ratio. The Poisson approximation is made in determining the variance of the expected deaths, that is, the variance is assumed to be equal to the mean of the expected deaths. The resultant X^2 is conservative, that is, it is less than the corresponding X^2 calculated using the binomial variance.

Step 8. The relative survival life table is calculated (1). The standard errors are estimated according to the method of Greenwood (10). For each year of survival, the following numbers are calculated, as illustrated in Table 3 (the data in Table 3 are limited to the first ten years of follow-up): LX, number starting each interval; WX, number of live withdrawals; UX, number lost to follow-up; OBS(DX), observed deaths; EXP(DX), expected deaths; OBS/EXP, observed/expected ratio; SURV, crude interval survival (1 to

$i+1$). RSR, relative interval survival; SERSR, standard error of RSR; CSURV, crude cumulative survival (0 to $i+1$); CRSR, relative cumulative survival; SECRSR, standard error of CRSR.

TABLE 2

PERSON-YEARS OF SURVIVAL IN A COHORT OF 761 WHITE FEMALES FOLLOWING TREATMENT FOR CARCINOMA OF THE ENDOMETRIUM ACCORDING TO AGE AND YEAR

Age	Year										
	1920-	1925-	1930-	1935-	1940-	1945-	1950-	1955-	1960-	1965-	Sum
25-					3.5	1.5	3.5	4.0	1.0		13.5
30-			0.5	2.5	0.3	7.5	5.5	13.0	10.0	0.5	39.8
35-			9.5	4.5	6.0	9.0	19.5	10.5	19.0	3.5	81.5
40	3.5	1.5	4.5	17.0	18.5	20.0	37.0	38.5	14.0	4.5	159.0
45-	11.3	14.0	6.3	15.8	54.0	71.8	69.3	50.0	55.5	3.5	391.3
50-	10.5	40.8	47.8	38.3	82.3	132.0	120.5	129.5	112.0	15.5	729.0
55-	14.0	53.3	82.3	104.8	95.8	178.5	256.0	237.8	165.0	27.5	1214.8
60-	5.8	51.3	96.0	123.8	166.8	159.0	295.8	346.0	263.5	36.0	1543.8
65-	4.0	26.3	63.8	112.5	117.8	204.3	208.8	343.3	347.0	49.0	1536.5
70-	0.8	19.3	45.3	52.8	100.3	161.5	209.0	203.5	329.5	64.5	1186.3
75-		2.3	19.0	31.3	37.5	90.0	141.5	185.8	158.0	37.0	702.3
80		1.5	1.0	12.3	17.5	21.5	63.8	95.5	106.0	14.5	332.0
85+			1.5	0.5		7.0	12.5	43.0	65.0	11.5	142.5
Sum	49.8	210.0	377.3	515.8	760.0	1063.5	1442.5	1740.3	1645.5	267.5	8072.0

TABLE 3

RELATIVE SURVIVAL RATIOS FOR 761 WOMEN FOLLOWING TREATMENT FOR CARCINOMA OF THE ENDOMETRIUM (SEE TEXT FOR DESCRIPTION OF DATA)

Year	LX	WX	UX	OBS(DX)	EXP(DX)	OBS	EXP	SURV	RSR	SCRSR	CSURV	CRSR	SECRSR
0-	761	1	0	91	14.4	6.3		.88	.90	.01	.88	.90	.01
1-	669	0	0	60	12.8	4.7		.91	.93	.01	.80	.83	.02
2-	609	1	0	40	12.7	3.2		.93	.95	.01	.75	.80	.02
3-	568	1	0	28	11.8	2.4		.95	.97	.01	.71	.77	.02
4-	539	0	0	18	11.5	1.6		.97	.99	.01	.69	.76	.02
5-	521	2	0	22	11.5	1.9		.96	.98	.01	.66	.75	.02
6-	497	5	0	11	11.7	0.9		.98	1.00	.01	.64	.75	.02
7-	481	12	0	10	12.7	0.8		.98	1.01	.01	.63	.75	.02
8-	459	24	0	11	12.7	0.9		.98	1.00	.01	.62	.75	.02
9-	424	20	0	11	12.0	0.9		.97	1.00	.01	.60	.76	.02
⋮													
Sum	—	296	0	465	263.6	1.8		—	—	—	—	—	—

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Steps 9–11. These steps are similar to steps 4–6. However, the person-years for each person are not distributed diagonally, as in Table 2, but horizontally according to *age* at entry into the cohort.

Steps 12–14. These steps are similar to steps 9–11. The person years are distributed horizontally according to *year* of entry into the cohort.

Modifications of Relative Survival

The numbers of cause-specific deaths expected in a cohort can be obtained if cause-specific mortality rates are substituted for total mortality rates in step 1. This technique has been used by others to determine whether excess mortality due to cancer has occurred in an industrial population (*11, 12*). Steps 1–14 are followed, with the only modification being in step 8. Persons dying from causes other than that being investigated are treated as live withdrawals in the year of their death. Thus, the total person-years of survival by the cohort is unchanged. However, only persons dying from the cause of interest are included in the observed deaths. The relative survival therefore is cause-specific.

If incidence rates are substituted for death rates in step 1, the expected number of incident cases of disease is obtained. Currently, the incidence rates of the Connecticut Cancer Registry from 1935–1962 are available (*13*).

Data Analysis Using Proportional Mortality

For each member of the study group, the following information is needed: sex, race, age, year and cause of death.

The steps in the computer program follow.

Step 1. The proportional mortality data matrix is read.

Step 2. The age-year-of-death distribution of all deaths in the study population is determined in five-year groupings.

Step 3. The age-time distribution of the observed deaths is determined.

Step 4. The age-time-specific expected deaths for each cause are calculated by multiplying the proportional mortality matrix times the age-time distribution of total deaths.

Step 5. Proportional mortality ratios are calculated by dividing the observed ratios by the expected ratios.

Step 6. The Mantel-Haenszel X^2 is calculated as described in step 7 above.

This procedure has been used in a study of the cause of death among alcoholics (*14*).

Some Technical Features

During one computer run, many causes of death may be evaluated in one cohort, one cause of death may be evaluated in many cohorts, or both. Several options

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exist as to the detail of calculation and output desired. When a single cohort is screened against all causes of death, the cohort data is read once and the person-years of survival are determined. Then each death rate matrix is multiplied by the person-years matrix to obtain the expected numbers of cause-specific deaths. Also, the observed deaths according to each cause are counted. When a single cause, usually all deaths, is screened against many cohorts, only the relative survival table is calculated and printed.

The program is written in Fortran IV and currently is in operation on the IBM 370/165 at the MIT-Harvard Computing Center. Most of the program has been compiled and is called as a subroutine. A short program (5-20 lines) must be written for each run to describe the input characteristics of the study cohort and any selections to be made. In addition, several control cards are needed to describe further characteristics of the cohort and to select the various options described above.

Comments

The major advantage of using rates from a standard population is that no formal comparison group need be assembled. In the case of retrospective cohort studies extending back many years, this is difficult. Further, since the standard rates are based on a large number of deaths, the rates are relatively stable.

The use of standard population rates has several disadvantages: characteristics of the study population which are related to death (or disease) may be different from those of the standard population The procedures described in this paper take account only of age, time, sex and race differences. No account can be made, for example, of the effect of cigarette smoking on differences in observed and expected rates. The effects of this problem may be studied in several ways. If available, a standard population which is relatively similar to the study population may be selected (*3*). An estimate of the maximum impact of confounding due to confounding variables can be made (*1, 15*). The best way to evaluate suspected causal relationships is to study them in diverse groups using diverse standard populations, or, if possible, to conduct cohort studies using a formal comparison group.

Another disadvantage arises if two or more study cohorts are compared to the standard population. If relevant demographic characteristics differ between the two study groups, inferences comparing the two groups may not necessarily be made by comparing their experience relative to the standard population (*16, 17*). For example, if relative survival is a function of age, and if two study cohorts have different age distributions, age-adjusted relative survival rates must be calculated. A second possibility is to compare the two groups directly, by using one group as the standard population and the other as the study population. This option is available in the program.

The primary disadvantages of studies using proportional mortality is that disease rates are not obtained. A proportional mortality greater than one may result from a

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high disease-specific death rate or a low death rate from other causes. However, a proportional mortality study is very economical in terms of time and money and may serve as a preliminary test of a causal hypothesis (3, 14). If suggestive results are obtained, a cohort study (retrospective or prospective) may be designed to provide a more definitive test of the hypothesis.

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