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INDIRECT STANDARDIZATION AND MULTIPLICATIVE MODELS FOR RATES, WITH REFERENCE TO THE AGE ADJUSTMENT OF CANCER INCIDENCE AND RELATIVE FREQUENCY DATA

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INTRODUCTION

THE OBJECT of standardization procedures is to summarize mortality or morbidity rates for the individual age groups or other strata of a population into a single index which indicates its position relative to other populations while accounting for differences in age structures. When both numerator and denominator data are available for all strata in each population, and when the aim is primarily descriptive, direct standardization [1] is the usual procedure. By combining age-specific rates with weights proportional to an external standard age distribution this technique produces a synoptic figure, the directly standardized rate, suitable for official publications. Comparisons of populations may be based on standardized rates compiled from several such sources, provided the same standard distributions have been used.

Situations often arise, however, in which either the age-specific data required for direct standardization are not available or, if available, the numbers of cases in certain age groups are so small that the rates are unstable and statistical significance is at issue. For the comparison of a specific set of populations under such conditions, Part I of this paper proposes the fitting of a multiplicative model to the two dimensional table of age-specific rates. This approach leads to versatile tests for the equality of population rates. When there are differences among the populations, efficient maximum likelihood estimates of those differences are obtained, provided the model holds. (This qualification is discussed below.) However the approach does not produce the sort of synoptic figure required for comparisons with other populations not included in the analysis.

The methodology proposed here may be considered as a refinement and extension of the method of 'indirect' standardization which produces the standardized mortality ratio (SMR) [1].

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Some of the techniques were previously suggested on empirical grounds by Mantel and Stark [2] while Clayton [3] has explored the connection with multiplicative models from a more theoretical viewpoint.

Three examples are given of the usefulness of the approach. The first is a comparison of colon cancer incidence among the counties of Sweden. While complete denominator data were available from published documents, cancer cases were classified by age and by county separately rather than simultaneously, making computation of directly standardized rates impossible. The proposed methods nevertheless led to an assessment of the geographical variation in incidence.

The second example examines breast cancer incidence among birth cohorts in Iceland. As is typical in cohort studies with a limited period of case ascertainment, information was lacking for many age-cohort cells and direct standardization of rates for each cohort was again impossible. However a pattern of secular increase in breast cancer incidence was established.

The third example concerns the comparison of relative frequencies of cancers occurring at several sites in the absence of population denominators. An extension of the multiplicative model used for the previous two examples, made in Part II of this paper, contains parameters interpretable as indirectly standardized *relative* mortality or morbidity ratios (SRMR). The SRMR provides an alternative to the directly age-standardized cancer ratio (ASCAR) proposed by Tuyns [4]. Consideration of other parameters in the model, and its goodness-of-fit, leads to a more thorough analysis of relative frequency data than has been given heretofore.

PART I: THE MULTIPLICATIVE MODEL FOR RATES

Denote by N_{ij} the number of individuals at risk in the jth age-category ($j=1, \ldots J$) of the ith population ($i=1, \ldots I$) and by D_{ij} the number of events (deaths from or new cases of cancer at a specific site(s) etc. depending on the application) occurring among those individuals in a specified time period. We assume that the populations are sufficiently large, and events sufficiently rare, that the data are well represented by the Poisson model: the N_{ij} are regarded as fixed numbers whereas the D_{ij} are assumed subject to random variation according to the Poisson distribution with expectation $E(D_{ij})=\lambda_{ij}N_{ij}$.

Standardization procedures combine the age-specific rates λ_{ij} into a summary index for each population which shows its position relative to the others. Use of a summary index, as opposed to separate comparison within each age group, is fully justified only if the age-specific rates display a certain consistency: viz. within the limits of statistical variation, the relative position of each population vis-à-vis age-specific mortality should remain constant over the J age groups.

If one population has higher rates than another among young persons, but lower rates among the elderly, use of a summary rate will obscure the differences.

A particularly simple mathematical model for the rate structure which satisfies this requirement of consistency is expressed in the equation

$$\lambda_{ij}=\theta_i\varphi_j, \tag{1}$$

whereby the age-specific rates are obtained from multiplicative contributions for the ith population (θ_i) and jth age group (φ_j). This model is over-parameterized in the

sense that if the sets of numbers θ_i and φ_j satisfy (1), the sets $\alpha\theta_i$ and $\frac{1}{\alpha}\varphi_j$ will do so also. Appropriate choices of the constant α to aid in interpretation will be discussed below.

While seemingly quite restrictive, this model is nevertheless a generalization of a more formal mathematical model [5] known to hold approximately for many types of cancer, especially of epithelial tissue. With this latter model the multiplicative effects φ_j for persons of approximate age t_j are assumed proportional to a power t_j^k. There is but a single parameter, k, to describe the age effect for cancer occurring at a specific site.

Reasons for a failure of the model to hold, in particular for cancer incidence data, would include a strong cohort effect, as with lung cancer, or lack of comparability of case reporting. Strong cohort effects could lead to the cross-sectional age incidence curves for the populations to be compared having different shapes when plotted on semi-log paper, in violation of the model. This situation warrants inclusion of birth cohort as an additional factor in the analysis, as is done below for breast cancer in a single population (Iceland). Non-comparability of case reporting might arise from variable underreporting in older age groups, or from different methods of case ascertainment, as with cervical cancer and screening programs. No amount of statistical manipulation can correct for such 'hidden' biases in the basic data collected.

On the other hand, if the model fits reasonably well, a clear advantage is gained for handling missing information, or as a means of making more precise comparisons by reducing the number of parameters.

There is a very close connection between the model (1) and log-linear models for contingency tables [6–8]. In the contingency table problem the λ_{ij} are usually regarded as cell occupancy probabilities in a 2-way classification of N individuals and equation (1) merely expresses the hypothesis of independence between the two axes of classification. The difference here is caused by the varying numbers N_{ij} of individuals at risk in each cell. Obvious generalizations may be made to more than two axes as has been done for the contingency table problem. Computational techniques are very similar.

Statistical analysis: by maximum likelihood

Estimates of the population and age effects θ_i and φ_j, tests for homogeneity among the populations, and evaluation of the goodness-of-fit of the model are all easily obtained from the ln-likelihood function

$$L=\sum_i D_{i+}\ln\theta_i+\sum_j D_{+j}\ln\varphi_j-\sum_i\sum_j\theta_i\varphi_j N_{ij}+\text{constant}. \tag{2}$$

Here $D_{i+}=\sum_j D_{ij}$ and $D_{+j}=\sum_i D_{ij}$ are the marginal totals of events occurring in each population and age category. The fact that (2) depends on the data through the D_{i+} and D_{+j} is important since these summary statistics are sometimes the only ones available in published tables, as is the case with the Swedish registry data. This restriction has often led to a use of indirect as opposed to direct methods of standardization, since the latter require knowledge of the individual D_{ij}. Of course a test of the adequacy of the model is possible only if the D_{ij} are known.

Maximum likelihood estimates (MLEs) of the parameters θ_i and φ_j may be obtained iteratively from the likelihood equations

$$D_{i+} = \theta_i \Sigma \varphi_j N_{ij},\ i=1, \ldots, I \text{ and} \tag{3}$$

$$D_{+j} = \varphi_j \Sigma_i \theta_i N_{ij},\ j=1, \ldots, J. \tag{4}$$

Initial values $\theta_i^{(1)}=1$ for θ_i are inserted in (4) to yield $\varphi_i^{(1)}=D_{+j}/N_{+j}$ as the initial estimate of φ_j. This is simply the crude rate in the jth age group, obtained by pooling the I populations. The second cycle leads to

$$\theta_i^{(2)} = D_{i+}/\Sigma_j \varphi_j^{(1)} N_{ij} \tag{5}$$

$$= D_{i+}/\Sigma_j \left(\frac{D_{+j}}{N_{+j}}\right) N_{ij}$$

and

$$\varphi_j^{(2)} = D_{+j}/\Sigma_i \theta_i^{(2)} N_{ij}. \tag{6}$$

Equation (5) will be recognized as the SMR for the ith population with the pooled death rates $\varphi_j^{(1)}$ being used as standards. The second cycle estimate $\varphi_j^{(2)}$ represents an adjustment to the pooled rate which takes account of the differing SMRs for the I populations.

After each cycle $n=1, 2 \ldots$ the estimates $\theta_i^{(n)}$ and $\varphi_j^{(n)}$ are inserted in (2) to determine the increase in the ln-likelihood L. The procedure terminates when L stabilizes or equivalently when the $\theta_i^{(n)}$ and $\varphi_j^{(n)}$ have settled down to their maximum likelihood values of $\hat{\theta}_i$ and $\hat{\varphi}_j$, respectively. Convergence, which is guaranteed by the results of [9], is quite rapid unless there are marked differences in rates among the populations and, at the same time, marked differences in their age distributions. Otherwise the SMRs obtained (5) in the second cycle will be a reasonable approximation to the final MLEs.

Mantel and Stark [7] suggest choosing the normalization constant α in such a way than when the φ_j, interpreted as (adjusted) age-specific rates, are applied to the pooled population at risk in each age category, the total number of events is as observed, i.e.

$$\Sigma\left(\tfrac{1}{\alpha}\hat{\varphi}_j\right) N_{+j} = D_{++}. \tag{7}$$

In other words, at convergence the $\hat{\theta}_i$ are multiplied by the factor

$$\alpha = \Sigma_j N_{+j} \hat{\varphi}_j / D_{++}, \tag{8}$$

and the φ_j are then divided by α. Numerical work shows that in cases of rapid convergence the numerator and denominator of (8) will not differ sufficiently to make this adjustment necessary.

Goodness-of-fit of the multiplicative model may be evaluated by likelihood methods (see examples) or by simply comparing the observed (D_{ij}) and expected ($\hat{D}_{ij}=\hat{\theta}_i\hat{\varphi}_j N_{ij}$) numbers of events in each population/age category according to the usual chi-square criterion $\Sigma(O-E)^2/E$. This has $(I-1)(J-1)$ degrees of freedom. Examination of the individual rates for consistency with (1) is also important.

An overall comparison of the I populations may be based on differences in the ln-likelihood function evaluated at the first and last cycles of the iteration procedure, i.e. when the θ_i are taken as unity or their maximum likelihood values, respectively (see examples).

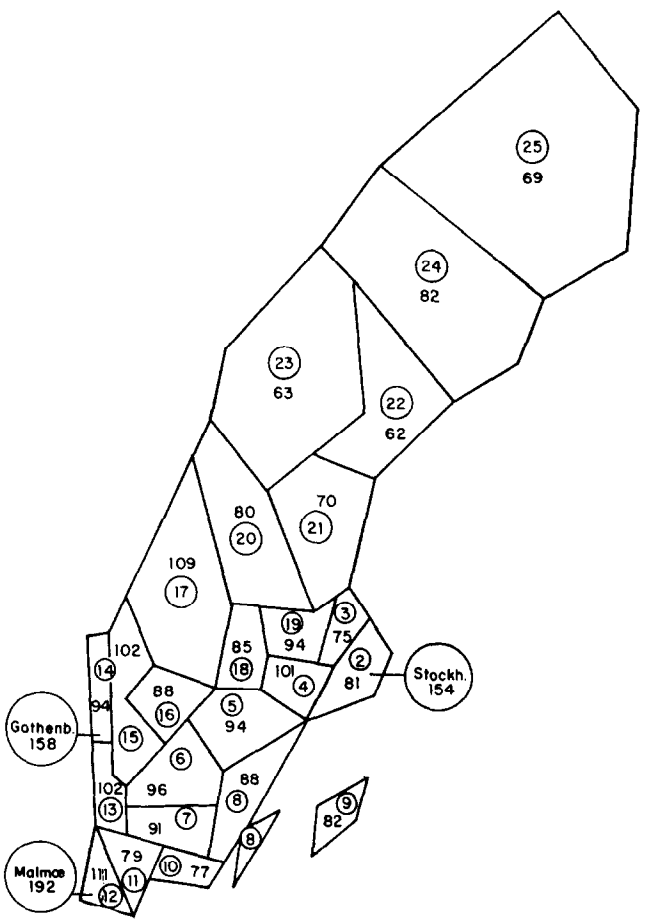

FIG. 1. The 27 counties of Sweden with age-adjusted incidence ratios (SMR) of male colon cancer 1959–1965, X100. Counties are identified by an encircled code number as in Table 1. Map of Sweden adapted from [10].

TABLE 1. RESULTS OF FITTING MODEL (1) TO SWEDISH DATA ADJUSTED SMRs BY COUNTY

Code	County	Cycle 1	Cycle 2*	Cycle 3	Cycle 4	Adjusted age-specific incidence rates of colon cancer for males, per 100,000 person-yr: Age group	Cycle 1†	Cycle 4
01	Stockholms (city)	1.000	1.536	1.539	1.539	0–4	0.1	0.1
02	Stockholms (county)	1.000	0.811	0.811	0.811	5–9	0.0	0.0
03	Uppsala	1.000	0.752	0.749	0.749	10–14	0.2	0.2
04	Södermanlands	1.000	1.015	1.015	1.015	15–19	0.6	0.6
05	Ostergötlands	1.000	0.938	0.938	0.938	20–24	0.8	0.8
06	Jönköpings	1.000	0.953	0.952	0.952	25–29	1.6	1.6
07	Kronobergs	1.000	0.912	0.910	0.910	30–34	2.3	2.2
08	Kalmar	1.000	0.884	0.883	0.883	35–39	3.7	3.6
09	Gotlands	1.000	0.821	0.819	0.819	40–44	6.7	6.5
10	Blekinge	1.000	0.771	0.770	0.770	45–49	9.6	9.4
11	Kristianstads	1.000	0.792	0.790	0.790	50–54	16.2	15.9
12	Malmö city	1.000	1.918	1.919	1.919	55–59	30.7	30.3
12a	Malmöhus	1.000	1.118	1.118	1.118	60–64	48.7	48.3
13	Hallands	1.000	1.024	1.023	1.023	65–69	79.6	79.3
14	Göteborgs (city)	1.000	1.582	1.585	1.585	70–74	121.3	121.1
14a	Göteborgs och Bohus	1.000	0.938	0.938	0.938	75–79	171.8	174.1
15	Alusborgs	1.000	1.020	1.020	1.020	80–84	201.1	205.7
16	Skaraborgs	1.000	0.878	0.877	0.877	85+	160.7	164.9
17	Värmlands	1.000	1.093	1.092	1.092			
18	Orebro	1.000	0.850	0.849	0.849			
19	Västmanlands	1.000	0.943	0.942	0.942			
20	Kopparbergs	1.000	0.801	0.802	0.802			
21	Gävleborgs	1.000	0.700	0.700	0.700			
22	Västernorrlands	1.000	0.623	0.623	0.623			
23	Jämtlands	1.000	0.632	0.631	0.631			
24	Västerbottens	1,000	0.822	0.823	0.823			
25	Nörbottens	1,000	0.692	0.694	0.694			
ln-likelihood		−35958.189	−35719.275	−35719.270	−35719.270			
Numerator of equation (8)		5709	5708.977	5710.152	5710.180			

*Unadjusted SMRs based on pooled age-specific rates.
†Age-specific rates for all of Sweden (pool of 27 counties).

Geographical study of colon cancer in Sweden

The problem which motivated the present methodological inquiry was that of comparing the incidence of colon cancer among the 27 counties of Sweden, using 1959–1965 data from the Swedish Cancer Registry [10]. While population denominators were given for each county and age group [10, Table 3], the numbers of cancer cases were given only by age [10, Table 6] or county [10, Table 8].

Table 1 shows the results of fitting the multiplicative model to data for males. Convergence was obtained after the fourth cycle. The SMRs computed using the pooled age-specific rates (cycle 2) are already close enough to the final values to suffice for practical purposes. There are major differences among the 27 counties, as indicated by taking twice the difference in ln-likelihoods for cycles 4 and 1 ($\chi^2_{26}=477.8$). When plotted on a map of Sweden (Fig. 1), it is clear that incidence is lowest in the northern counties, becoming higher as one proceeds southward, and is highest of all in the three urban areas (circles on map) of Malmö (SMR=1.92), Göteborg (SMR=1.58), and Stockholm (SMR=1.54).

Cohort analysis of Iceland breast cancer incidence

The multiplicative model is also useful for the analysis of cancer incidence rates by birth cohort, as shown by Bjarnason *et al.* [11] in their study of breast cancer in Iceland. Table 2 gives the observed and expected number of cancer cases and estimated person-years at risk by age-group and year of birth in 10 yr intervals from 1850 to 1949. An important feature of this table is the large number of empty cells ($N_{ij}=0$) due to the fact that collection of cases was limited to the years 1910–1971 inclusive. Such cells are readily incorporated into the estimation procedure (equations (3-6)) although of course they contribute no information to the ln-likelihood functions.

Convergence of the estimates was slower with these data than previously for the reasons already mentioned: the pooled age incidence data for the younger ages were based on later cohorts and there were large differences among cohorts. However by the 10th iteration the fitted incidence ratios θ_i and age-specific rates φ_j had converged to three significant digits. By this time the numerator (1363.4) and denominator (1305) of equation (8) differed sufficiently that the correction constant α was applied to the final values (Table 3). Comparing the ratios for the 11 birth cohorts shows a steady secular trend in breast cancer incidence, with the rates for the 1930–1939 cohort about 10 times those for 1840–1849. The exceptionally high SMR of 4.350 for the latest cohort (1940–1949) is unreliable as it is based on only seven cases.

Goodness-of-fit of the multiplicative model was excellent, with the ln-likelihood test yielding 49.65 on 54 degrees of freedom. Comparison of observed and expected (Table 2) numbers of cases according to the standard chi-square criterion $\Sigma(O-E)^2/E$ yielded 48.97, with contributions from individual cells exceeding the 95 percentile value of 3.84 only in the youngest age group for the 1890 cohort.

The crude age-specific incidence curve (Fig. 2) is clearly flatter than the corresponding fitted curve, a reflection of the higher age-specific incidence in the recent cohorts, and a lower incidence in the older cohorts. A similar but less marked tendency can be seen in Table 1 for the Swedish data, indicating a relatively older population in the counties with lower incidence. Further discussion of the interpretation of the model for the Iceland data is given in [11].

TABLE 2. OBSERVED AND EXPECTED NUMBERS OF FEMALE BREAST CANCER CASES IN ICELAND DURING 1910–1971 BY AGE AND YEAR OF BIRTH, WITH APPROXIMATE PERSON-YEARS AT RISK*

Age	Year of birth 1840–1849	1850–1859	1860–1869	1870–1879	1880–1889	1890–1899	1900–1909	1910–1919	1920–1929	1930–1939	1940–1949
	Observed cases/Expected cases/Person-years										
20–24						2 0.42 41,380	– 0.52 43,650	1 0.74 49,810	1 0.85 58,105	1 1.30 57,105	2 3.16 76,380
25–29						– 1.10 39,615	2 1.37 42,205	1 1.96 48,315	1 2.27 56,785	5 3.47 55,965	5 3.83 33,955
30–34					1 2.38 29,150	1 3.37 38,430	3 4.22 40,810	7 6.12 47,490	12 7.06 55,720	10 10.84 55,145	
35–39					6 6.01 27,950	11 8.61 37,375	9 10.84 39,935	14 15.88 46,895	20 18.30 54,980	14 14.36 27,810	
40–44				7 10.13 25,055	14 12.28 27,040	22 17.72 36,400	25 22.56 39,355	29 33.11 46,280	37 38.21 54,350		
45–49				21 15.21 24,040	11 18.68 26,290	29 27.03 35,480	33 34.75 38,725	57 51.05 45,595	24 28.29 25,710		
50–54			15 9.71 22,890	8 15.88 23,095	22 19.25 25,410	27 27.96 34,420	38 36.09 37,725	52 53.41 44,740			
55–59			10 10.61 21,415	15 17.22 21,870	22 21.43 24,240	26 31.45 33,175	47 40.58 36,345	31 29.70 21,320			
60–64		8 5.68 17,450	11 10.44 19,765	17 17.01 20,255	23 21.47 22,760	31 32.06 31,695	38 41.34 34,705				
65–69		8 7.71 15,350	10 14.44 17,720	24 23.67 18,280	30 30.32 20,850	53 46.16 29,600	26 28.71 15,635				
70–74	5 2.92 9,965	3 5.14 12,850	10 9.74 15,015	18 16.21 15,725	22 21.23 18,345	30 32.77 26,400					
75–79	1 3.62 8,175	7 6.64 11,020	11 12.80 13,095	26 21.83 14,050	32 28.75 16,480	17 20.37 10,885					
80–84	5 4.46 7,425	8 8.85 10,810	17 16.28 12,260	32 31.19 14,780	31 32.23 13,600						

*From Bjarnason *et al.* [11]. Minor corrections have been made to the denominators as given by these authors for the age group 25–29.

TABLE 3. RESULTS OF FITTING THE MULTIPLICATIVE MODEL TO THE DATA IN TABLE 2 (10 ITERATIONS)

(A) Adjusted SMR by cohort
Year of birth

1840–	1850–	1860–	1870–	1880–	1890–	1900–	1910–	1920–	1930–	1940–
0.252	0.345	0.558	0.886	0.995	1.067	1.257	1.568	1.541	2.392	4.350

(B) Adjusted age-specific incidence rates per 100,000 person-years
Age

20–	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–
1.0	2.6	8.2	21.6	45.7	71.4	76.1	88.8	94.8	146.1	116.3	175.3	238.1

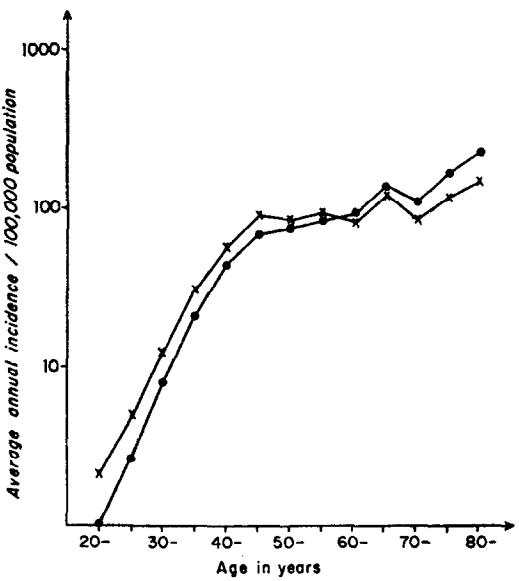

FIG. 2. Crude (X) and fitted (•) age-specific incidence rates for female breast cancer in Iceland, 1911–1972.

PART II: EXTENSION OF THE MULTIPLICATIVE MODEL FOR ANALYSIS OF RELATIVE FREQUENCY DATA (RATIO STUDIES)

For many collections of cancer cases, particularly individual hospital series, it is impossible to define precisely the population in which those cases arose. Or, even if the population is well defined, its age structure may not have been determined. This means that age-specific rates cannot be calculated. Nevertheless the collection may be very interesting from an epidemiological point of view because an unusually high or low proportion of the cases seem to be occurring at a particular site. There is a need, therefore, for methods of comparing several such collections, while taking account of possible differences in age structures. One such method has been proposed by Tuyns [4]. Analogous to the directly standardized rate, this is known as the age standardized cancer ratio (ASCAR).

An alternative approach to such data may be made via an extension of the multiplicative model considered above. One hypothesizes that the frequency D_{ijk} of cases occurring at the kth of K sites in the jth age group of the ith population is again a Poisson variate with expectation

$$E(D_{ijk})=N_{ij}\theta_{ik}\varphi_{jk}. \tag{9}$$

In other words, the previously described multiplicative model, in which the shape of the age incidence curve was assumed constant over the I populations, is assumed to hold independently for *each* of the K sites considered. However now the population denominators N_{ij} are unknown and must themselves be estimated (up to multiplicative constants) from the observed frequencies D_{ijk}.

The model (9) is equivalent to the hypothesis of 'no three-dimensional interactions' in the three-dimensional table of frequencies. An iterative method of maximum likelihood fitting of this and similar models has been described by many authors for example Bishop [6]. The fitted (expected) frequencies $\hat{D}_{ijk}$ satisfy exactly the multiplicative relationship (9) and, at the same time, have marginal totals which agree with the D_{ij+}, D_{+jk} and D_{i+k} observed. Most general purpose computer programs* written to perform these calculations decompose the fitted frequencies into the product

$$\hat{D}_{ijk}=D\mu_i^A\mu_j^B\mu_k^C\mu_{ij}^{AB}\mu_{ik}^{AC}\mu_{jk}^{BC}. \tag{10}$$

$D=D_{+++}$ is the total number of cases while the remaining terms represent first and second order multiplicative interactions among the factors A, B, C corresponding to the three dimensions of the table (here A=population, B=age, C=site). These are normalized so that their product over the appropriate indices is unity, e.g.

$$\prod_{i=1}^{I}\mu_i^A=\prod_{i=1}^{I}\mu_{ij}^{AB}=\prod_{j=1}^{J}\mu_{ij}^{AB}=1.$$

The term μ_{ik}^{AC} corresponds to an age standardized relative morbidity ratio (SRMR) in that it represents the position of the ith population for cancer incidence at the kth site relative to its position for other sites. It is of course impossible from relative frequency data to estimate differences in overall incidence rates since these are confounded with differences in population size. Similarly the terms μ_{jk}^{BC} give the relative shape of the age incidence curve for the kth cancer site, which is assumed constant over the I populations by the model (9). Departures from this hypothesis can be tested by ln-likelihood or by comparing the observed and fitted frequencies according to the usual $\Sigma(O-E)^2/E$ chi-square criterion. This has $(I-1)(J-1)(K-1)$ degrees of freedom provided there are no zero two-dimensional marginal totals. Inspection of the nature of the discrepancies $O-E$ is also important.

Application of the SRMR to comparisons among three populations

Table 4 shows the data from the Johannesburg Bantu [12], Singapore Chinese [13], and Swedish [14] populations analyzed in [4], except that the first three age groups have been pooled so as to avoid an excess of cells with zero entries. This yields a three-dimensional table with $I=3$ populations, $J=6$ age groups, and $K=6$ sites, one of which is a composite of 'all other' sites. Seven cycles of iteration were required to fit the

*The program used here was written by Dr. David Sylwester of the University of Vermont.

multiplicative model (9) so that all observed and expected two-dimensional marginal totals agreed to within 0.05.

Comparing the observed and fitted (or expected) values in Table 4 indicates a clear departure from the model. The chi-square goodness-of-fit statistic is equal to 166.1 on 48 degrees of freedom,* with the major contributions being from the three sites liver, brain+nervous system (BNS), and oesophagus. Inspection of the individual observed and expected values shows that in all three cases the shape of the Swedish age-incidence curve is lower initially and higher thereafter compared to that for the other two populations, except that the Bantu show an exceptionally high number (8) of oesophageal cases over 75 yr.

TABLE 4. OBSERVED AND EXPECTED* NUMBERS OF CANCER CASES OCCURRING AMONG MALES IN 3 POPULATIONS BY SELECTED SITES AND AGE

Age	0–		35–		45–		55–		65–		75–	
Site (ICD)	O	E	O	E	O	E	O	E	O	E	O	E
A. Bantu-Johannesburg (1953–1955)†												
146 Nasopharynx	4	1.5	1	2.3	0	1.6	1	0.4	0	0.1	0	0.0
150 Oesophagus	0	2.0	12	9.7	25	20.9	6	11.4	2	6.4	8	2.6
155 Liver	36	27.6	34	30.7	31	37.3	10	14.2	10	9.5	2	3.7
177 Prostate	0	0	0	0.3	3	3.1	7	5.2	8	7.9	3	4.4
193 Brain and NS	9	5.4	1	2.0	0	1.8	0	0.5	0	0.1	0	0.0
All other (140–205)	47	59.5	55	58.0	86	80.2	46	38.2	29	24.8	7	9.2
B. Chinese-Singapore (1950–1961)‡												
146 Nasopharynx	120	118.8	227	221.7	226	228.1	105	107.2	21	21.9	1	2.1
150 Oesophagus	10	7.3	47	45.1	142	141.6	146	146.7	49	50.6	6	8.6
155 Liver	40	46.1	68	64.0	139	113.6	70	82.3	24	33.5	4	5.5
177 Prostate	0	0	0	0.2	1	2.3	10	7.2	1	6.8	6	1.6
193 Brain and NS	55	34.1	7	15.8	13	21.1	7	11.9	3	1.9	0	0.2
All other (140–205)	315	333.7	404	406.2	806	820.4	760	742.6	311	294.2	47	45.9
C. Sweden (1961)§												
146 Nasopharynx	0	3.7	2	6.0	12	8.3	11	9.4	7	5.9	4	2.8
150 Oesophagus	0	0.8	0	4.2	13	17.5	50	43.9	53	46.9	36	38.7
155 Liver	7	9.4	4	11.4	8	27.1	64	47.4	69	60.0	51	47.7
177 Prostate	0	0	2	1.5	30	28.6	212	216.6	634	628.3	709	712.0
193 Brain and NS	57	81.4	43	33.1	69	59.1	86	80.6	39	40.0	19	18.8
All other (140–205)	336	304.8	330	324.8	890	881.4	1900	1925.1	2344	2364.9	1782	1780.9

*Expected values calculated under the multiplicative model (9) by iterative fitting to all 2-dimensional marginal tables using a computer program written by Dr. David Sylwester, University of Vermont.

†Data from [12].

‡Data from [13]. Forty-eight cases of unknown age excluded.

§Data from [14].

*There are 48 rather than $50=(I-1)(J-1)(K-1)$ degrees of freedom because of the 0 margina total for prostate cases under 35 yr.

The relative shapes of the age-incidence curves estimated from the model are shown in Fig. 3. That for 'all other sites' is essentially flat as would be expected since these are numerically dominant. The shapes indicate that BNS and nasopharyngeal tumors tend to occur relatively earlier in life than others, while tumors of the prostate and oesophagus occur later. The shape of the liver cancer curve is about the same as that for all tumors. These findings are well known from studies of actual incidence rates.

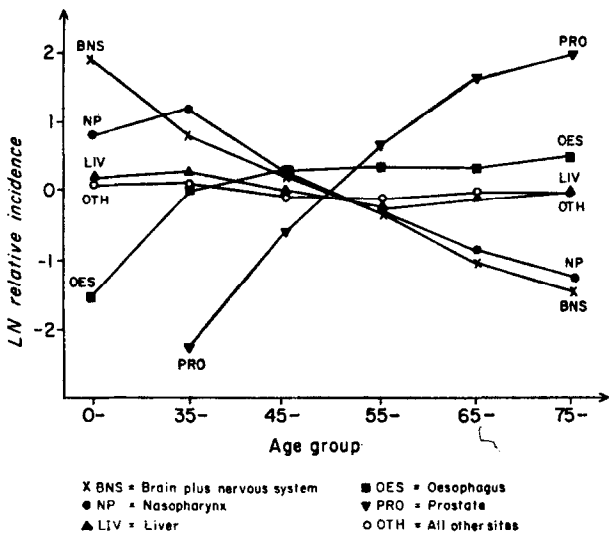

FIG. 3. Relative shapes of age incidence curves for six different cancer sites; natural logarithmic (LN) scale.

In spite of the apparent lack-of-fit, it is instructive to compare the SRMRs estimated from the model (Table 5A) with other summary statistics. The results indicate that, relative to whatever differences may exist for all sites combined, the Chinese have more nasopharyngeal cancer, the Bantu have more liver cancer, and both groups have more oesophageal cancer than do the Swedes. Prostate and BNS cancers are relatively more prominent for the latter population as are 'all other' cancers.

Although compared originally in terms of relative frequencies, population denominators were available for each of the three populations studied. These permitted standardized ratios of incidence rates (SMRs) to be calculated independently for each site according to the iterative methods described previously. Results of these calculations are shown in Table 5(B), where the SMRs for each site have been normalized so as to multiply to unity* and thus facilitate comparison with Table 5(A). There is a remarkable agreement between the two sets of figures, indicating that overall cancer incidence is not too dissimilar among the three populations. In general agreement would be expected only between the ratio of SRMRs at two different sites and that same ratio of SMRs.

*This is a different type of normalization than suggested by equations (7) and (8).

TABLE 5. AGE-STANDARDIZED ABSOLUTE (SMR) AND RELATIVE (SRMR) INCIDENCE RATIOS AMONG 3 POPULATIONS FOR CANCER AT SELECTED SITES (MALES ONLY)

Population	Site (ICD) Naso-pharynx 146	Oeso-phagus 150	Liver 155	Prostate 177	Brain + NS 193	All other 140–205
	A. SRMR: Relative ratio calculated without population denominators					
Johannesburg Bantu	0.37	1.86	2.54	1.81	0.46	0.69
Singapore Chinese	6.40	1.54	0.95	0.19	0.65	0.86
Sweden	0.42	0.35	0.42	2.91	3.33	1.69
	B. SMR: Absolute ratio using population denominators*					
Johannesburg Bantu	0.39	1.72	2.59	1.60	0.58	0.73
Singapore Chinese	6.97	1.60	0.96	0.15	0.63	0.88
Sweden	0.37	0.36	0.40	4.13	2.77	1.56

*Calculated according to methods outlined in Part 1 of paper, but with SMRs normalized to multiply to unity in each column.

Comparison of the SRMR with the ASCAR

The directly standardized ASCAR of Tuyns [4] consists of a weighted mean of the age-specific relative frequencies (D_{ijk}/D_{ij+}) for each site (k) and population (i), the weights being proportional to the age distribution of a standard collection of cancer cases. As with directly standardized rates, this method has the advantage of simplicity and of producing a synoptic figure for use in making universal comparisons; it has the disadvantage of an arbitrary weighting system which is insensitive to the varying degrees of statistical precision in the age-specific quantities. For this reason an analysis based on the model (9), producing the SRMR, is preferable for making comparisons among particular sets of populations, especially when statistical significance is at issue. Of course the same reservations noted above regarding comparability of the populations vis-à-vis diagnostic practices, completeness of reporting, etc. would apply.

Under the multiplicative model (1) for rates, ratios of SMRs and ratios of directly standardized rates for two populations (say 1 and 2) will tend to estimate the same quantity, namely θ_1/θ_2. This result does not carry over to the relative frequency situation. Under the model (9) ratios of SRMRs and ASCARs (appropriately normalized) for different populations will tend to estimate the same quantity only if the shapes of the age incidence curves for different sites are identical. In this case the relative frequencies in each population will be approximately constant from one age group to the next.

In spite of these quantitative differences, the ASCAR and SRMR will of course lead to similar conclusions when populations evidence such extreme differences as in the example. Table 6A shows ASCARs calculated for the data of Table 4 using

Tuyns' [4] 'European' age-distribution of cancer cases.* Table 6B shows relative frequencies calculated from rates which were directly standardized to the 'European' age-distribution [15]. Both sets of figures were adjusted so that the values for the three populations at each site would multiply to unity, thus permitting comparison with Table 5. There is again fairly good agreement between Tables 6A and 6B. Comparing Table 5 and 6, however, shows that the SRMR approach leads to estimates of population differences which are somewhat smaller for nasopharynx, oesophagus, and liver, and larger for the remaining sites, as compared to the ASCAR.

TABLE 6. RELATIVE FREQUENCIES (IN PER CENT) OF CANCER AT SELECTED SITES IN 3 POPULATIONS (MALES ONLY), DIRECTLY STANDARDIZED TO A 'EUROPEAN' POPULATION; (VALUES NORMALIZED TO MULTIPLY TO ONE IN EACH COLUMN ARE SHOWN IN PARENTHESES)

	Site (ICD)						
Population	Naso-pharynx 146	Oeso-phagus 150	Liver 155	Prostate 177	Brain+ NS 193	All other 140–205	Totals
	A. Ascar: Directly standardized frequencies, no population denominators						
Johannesburg Bantu	1.01 (0.59)	12.49 (2.35)	21.59 (3.24)	8.64 (1.57)	1.50 (0.58)	54.77 (0.83)	100.0
Singapore Chinese	12.33 (7.22)	9.57 (1.80)	7.26 (1.09)	1.66 (0.30)	2.08 (0.81)	67.09 (1.01)	100.0
Sweden	0.40 (0.23)	1.25 (0.23)	1.88 (0.28)	11.44 (2.09)	5.44 (2.12)	79.59 (1.20)	100.0
	B. Relative frequencies determined from directly standardized rates, using population denominations						
Johannesburg Bantu	0.69 (0.47)	13.68 (2.25)	19.27 (2.89)	9.94 (1.66)	0.68 (0.51)	55.75 (0.84)	100.0
Singapore Chinese	12.22 (8.44)	10.77 (1.77)	7.53 (1.13)	1.32 (0.22)	1.09 (0.82)	67.07 (1.02)	100.0
Sweden	0.36 (0.24)	1.53 (0.25)	2.05 (0.31)	16.28 (2.72)	3.14 (2.37)	76.64 (1.16)	100.0

CONCLUSION

A simple multiplicative hypothesis, known to be approximately satisfied for a variety of cancer incidence data, has led to refinements in the procedure for indirect standardization of rates and to an analysis of relative frequency data based on a type of indirectly standardized frequency ratio (the SRMR). We believe that the proposed techniques provide a valuable tool for epidemiologists and statisticians engaged in the comparative study of particular populations. The added computational complexity is well worth the return of increased amounts of information gleaned from the data and greater confidence in the conclusions drawn. However it must be emphasized that no amount of statistical sophistication can overcome biases in the basic data collected.

*The minor discrepancies between corresponding entries in Table 6A and Table III of [4] are due to the first three age groups 0–14, 15–24, and 25–34 having been collapsed into one.

SUMMARY

By assuming that a simple multiplicative relationship exists between the age-specific mortality or morbidity rates for several populations, one is led to comparison of these populations using indirectly standardized mortality or morbidity ratios (SMR) where the age-specific rates for all populations combined are used as standards. Adjustments to these ratios are needed in case of large differences among the populations in both age-specific rates and age structures. This method is appropriate when insufficient data are available for direct standardization or when numbers of cases in individual age groups are so small as to make directly standardized rates unstable. It is oriented towards the internal comparison of specific sets of populations rather than production of synoptic figures for official publication. Extensions of the multiplicative hypothesis to the simultaneous analysis of multiple causes of mortality or morbidity suggest the use of a standardized relative mortality ratio (SRMR) for making comparisons when age-specific population denominators are not available. These methods are used to study several sets of cancer incidence and relative frequency data.

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