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Statistical modeling of epidemiologic data¹

by Markku Nurminen LSc, Pertti Mutanen, MSc²

NURMINEN M, MUTANEN P. Statistical modeling of epidemiologic data. *Scand j work environ health* 6 (1980) 146—152. The application of statistical modeling to epidemiology may help suggest a form for the mechanism of exposure action. But distinguishing between the entertained biological models is often difficult due to both inadequacies in epidemiologic studies and inaccuracies in the verbal specifications of the hypothesized interaction mechanisms. For example, the independent and interactive effects of asbestos and smoking on the production of lung cancer have not yet been fully established. In the present communication an analysis of illustrative data from a hypothetical case-compeer study was attempted with the estimation of rate ratios and the use of a log-linear model fitting technique. These analyses allow a parametric representation of the testable models. For adequate material they might provide tentative insight as to whether the data would conform more closely to an additive model than to a multiplicative one or to some other advocated pattern of action.

Key terms: case-compeer (case-control) study, contingency table, interaction (association), log-linear models, rate ratios, stratified analysis.

¹ Definitions of terms used in this article: *contingency table* is a frequency table in which the contingent observation data are stratified by, ie, divided according to, two or more variables. *First-order* or *two-factor interaction* is the reciprocal action of a pair of qualitative variables forming a two-way contingency table; it is used synonymously with *association*. *Second-order* or *three-factor interaction* describes the mutual relationship of a triplet of variables in a three-way contingency table. *Synergism (antagonism)* is the simultaneous action of separate agents which, together, have a greater (less) total effect than the sum of their individual effects. A *log-linear model* postulates that the logarithm of the expected values of the observations in a contingency table are given by a linear combination of a number of parameters. *Hierarchical model* is such that, whenever a higher order effect is included in the model, the lower order effects composed from variables in the higher effect are also included.

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Applying a statistical model to epidemiologic data to test old and generate new biological models for the interaction of disease agents has been found to be useful, eg, in the specific area of carcinogenesis research (9). A known example of the problem at issue is the syncarcinogenesis of tobacco smoke and asbestos dust in the etiology of lung cancer.

At least three mechanisms (models) have been assumed to describe the existing epidemiologic data in asbestos-smoking interaction (7). In the first model the two factors act as independent causes and their joint effect is obtained if the reference category or base-line incidence rate of lung cancer is added to the excess over the base line due to asbestos. In addition the excess due to smoking can operate independently to produce lung cancer, but, when they occur together, their combined effect is synergistic, ie, more than additive. This model may be specified by different parametrizations. One with a wide applicability is constructed in a multiplicative fashion; the combined effect of the two factors is equal to the product of their

separate independent effects (multiplicative model).

It should be noted that the meaning of statistical independence depends on the scale of measurement or, equivalently, on the chosen model. Thus, eg, independence under the multiplicative model would imply synergism under the additive model (on a linear scale). According to the third and more complex model, smoking is a cause of lung cancer, but asbestos exposure is a cause only when the smoking factor is also present, and their combined effect is (usually much) greater than that of smoking alone. In this situation smoking is necessary for the effect of asbestos. We have called this model "smoking-synergistic" with no "effect" for asbestos on its own.

The majority of existing evidence favors the multiplicative model, but the distinction between these models is subtle.

Stratified analysis

For simplicity we have chosen artificial data from a case-compeer (case-control) study with two dichotomous study variables as the example. Table 1 shows the illustrative data for all 1,000 cases stratified by the two factors under investigation

(such as occurrence of asbestos fibers in the lungs and smoking history). These data would allow us to study the possible two- and three-factor interactions on the development of lung cancer.

When table 1 is collapsed over the smoking variable, the finding of larger numbers in the lungs of cancer cases than their compeers is highly significant at the 0.1 % level ($\chi^2 = 31.8$, $df = 1$). The rate ratio (RR) estimate can be calculated with the use of Bayes' theorem and prior information on the overall lung cancer rate (6); the RR estimate is calculated to be 2.3. The proportion of deaths from lung cancer (ICD 162) was, eg, in Finland in 1966, only 1.6 % of all deaths; therefore the exposure-odds ratio (a measure not utilizing available information for the overall rate) closely approximates the corresponding ratio of posterior lung cancer rates (given exposure). The 95 % confidence limits for this RR can be based on the value of the chi-square statistic used in significance testing (4); these limits are computed to be 1.7 and 3.1, which would indicate again the clear statistically significant increase in rate. The association between smoking habit and lung cancer is statistically highly significant ($\chi^2 = 154.1$, $df = 1$, $p < 0.001$). The corresponding RR estimate is 8.1 (5.8—11.3).

Table 1. Distribution of the lung cancer and compeer cases by occurrence of asbestos fibers in the lungs and smoking habits^a and the rate estimates for different exposure categories.

	Asbestos fibers present		Asbestos fibers absent		Total
	Smokers	Non-smokers	Smokers	Non-smokers	
Lung cancer cases	370	30	90	10	500
Compeer cases	200	120	90	90	500
Estimate of the exposure category specific rate ^b	2.92 %	0.40 %	1.60 %	0.18 %	
Estimate of rate ratio ^c	16.2	2.2	8.9	1.0	

^a Hypothetical data.

^b Estimated rate of lung cancer (posterior probability) = $1/[1 + \{(1 - R)/R\} (E_0/E_1)]$, where $R = 1.6$ % equals overall rate of lung cancer, ie, proportion of all deaths, E_1 = exposure rate among cases, and E_0 = exposure rate among compeers.

^c Rate ratio denotes the ratio of the rate among those in the combined exposure category to the rate among nonsmokers without asbestos fibers in the lungs (ratio of corresponding posterior probabilities).

Table 2. Percentage distribution of the lung cancer and compeer cases by smoking habits and occurrence of asbestos fibers in the lungs and the results of the significance and effect estimation.

	Smokers		Nonsmokers	
	Asbestos fibers present	Asbestos fibers absent	Asbestos fibers present	Asbestos fibers absent
Lung cancer cases	80 %	20 %	75 %	25 %
Compeer cases	69 %	31 %	57 %	43 %
	$\chi^2 = 12.8$ df = 1 p < 0.001		$\chi^2 = 4.5$ df = 1 p < 0.05	

Table 3. Percentage distribution of the lung cancer and compeer cases by occurrence of asbestos fibers in the lungs and smoking habits and the results of the significance testing and effect estimation.

	Asbestos fibers present		Asbestos fibers absent	
	Smokers	Non-smokers	Smokers	Non-smokers
Lung cancer cases	92 %	8 %	90 %	10 %
Compeer cases	62 %	38 %	50 %	50 %
	$\chi^2 = 97.0$ df = 1 p < 0.001		$\chi^2 = 44.8$ df = 1 p < 0.001	

As noted by Saracci (8) in a review of epidemiologic studies, a necessary condition for data to follow a multiplicative model is the constancy of RR due to asbestos for both smoking categories. The smokers' highly significant RR of 1.8 (1.3—2.5) is fairly close to that estimated for the nonsmokers [RR = 2.2 (1.1—4.6)], a finding which would demonstrate that smoking did not amplify the magnitude of the estimate of the effect of the asbestos factor. It is also evident from an inspection of the percentage distribution given in table 2.

Table 3 shows the percentage distribution of the lung cancer and compeer cases by occurrence of asbestos fibers in the lungs and smoking habits. The smokers' RR of lung cancer is 7.4 (5.0—11.0) among cases with asbestos fibers, but again an estimate of nearly the same magnitude is obtained among those cases without asbestos fibers [RR is 9.0 (4.7—17.1)].

Next we have further examined the relative adequacies of the compared models with reference to the imaginary data in table 1.

Estimates of the RR of lung cancer for the combination of smoking habit and the finding of asbestos fibers in the lungs can be derived from the estimated exposure category-specific rates of cases and compeers, again via Bayes' theorem. These RRs (posterior probabilities) are shown in the lower part of table 1. Non-smokers without asbestos fibers in their lungs are the reference category. In the quantitation of interaction, a convenient index development by Rothman (7) is "the ratio of the observed effect with combined exposure to that effect expected with independently acting causes operating jointly." This is an index of synergism if its value exceeds one and of antagonism if less than one; if equal to one it represents causes acting independently. The

relative excess risk associated with the presence of asbestos fibers, obtained by subtracting the reference category RR, is $2.2 - 1.0 = 1.2$. Similarly, the excess risk attributable to smoking is 7.9. Cases with both exposures have a relative excess risk of 15.2, whereas $1.2 + 7.9 = 9.1$ would be expected if these causes acted independently. The point estimate of the index of interaction is $15.2/9.1 = 1.67$, indicating some amount of synergism and departure from the additive model. An approximate 95 % interval estimate can be obtained for this index if the upper and lower limit is considered to be (7):

$$\exp [\log(1.67) \pm 1.96(\text{SE})/1.67],$$

based on a log-Gaussian sampling distribution. The standard error (SE) of the index is approximated with the use of Woolfian type estimators for the sample variances and covariances of the category-specific RRs. We obtain an interval of 0.8—3.4; thus in our example we can not be very confident that synergism actually exists, because the interval includes the value 1. For small numbers this method yields unstable estimates.

If interaction were assessed with the multiplication of the RRs as the criterion, these data would suggest a somewhat weaker than multiplicative effect, since the RR expected would be $2.24 \times 8.9 = 19.9$, whereas an RR of only 16.2 was observed. The ratio of observed RR to expected RR (0.81) measures the joint effect, in a *multiplicative sense*, of smoking and asbestos. (This ratio could equivalently be obtained if the smokers' RR were divided with that of the nonsmokers in table 2.) Since this ratio produced a value of slightly less than one, the two factors cannot be said to exert fully independent multiplicative effects in producing lung cancer.

Under the additive model we can, instead, expect an RR of 10.1 for the joint effect of these two carcinogens. Hence we might conclude that the data conform more likely to a multiplicative model than to the additive one and that the amount of synergism present very probably lies in a closer proximity to independence under the multiplicative model than under the additive model.

The incompatibility of the contingent

data with the smoking-synergistic model is seen in that the RR for the nonsmoking cases with asbestos fibers in the lungs was 2.2 instead of the hypothesized value of 1.0. This model is nonspecific in that it merely states the existence, and not the degree, of synergism. In other words, it is only supposed that the RR for cases with both exposures is greater than that for those who only smoked. The model does not specify, eg, that the combined exposure category-specific RR of 16.2 should be twice as large as that of the smoking cases with no trace of asbestos exposure (8.9).

Since none of the three competing models seemed to be fully capable of explaining the interrelations in the made-up data, a more formal manner of model specification and a more systematic approach to model search was deemed desirable.

Log-linear analysis

We have reanalyzed the data using a log-linear model fitting and testing technique (5). These models rely upon a particular approach to the definition of interaction between or among variables in multidimensional contingency tables; the expected cell values of the table are simply the product of marginal probabilities. As a result, the models are linear on a logarithmic scale — hence the label log-linear models. An algorithm in Standard Fortran for the estimation of the expected cell frequencies with the iterative scaling procedure is given by Haberman (2).

In hierarchical log-linear models for complete contingency tables the logarithm of the expected values ($\log F$) of the frequencies of the factorial table is assumed to satisfy an additive model similar to that encountered in an analysis of variance. In a fully parametrized model, for our example of a $2 \times 2 \times 2$ table,

$$\log F = M + C + S + A + CS + CA + SA + CAS,$$

where M = overall mean, C = main effect of variable "caseness," S = main effect of variable "smoking," A = main effect of variable "asbestos," CS = caseness-smoking interaction effect, CA = caseness-asbestos interaction effect, AS = asbestos-

Table 4. Analysis of the deviance for interaction between lung cancer, asbestos fibers in the lungs and smoking habits.^a

Number	Model terms ^{b, c}	Deviance ^d G ²	Degrees of freedom ^e	p-value
0	CA, CS, AS, CAS ^f	0	0	..
1	CA, CS, AS ^g	0.2	1	NS
2	CA, CS ^g	8.0	2	< 0.025
3	CA, AS	150.8	2	< 0.001
4	CS, AS	17.3	2	< 0.001
5	CA	173.6	3	< 0.001
6	CS	40.1	3	< 0.001
7	AS	182.9	3	< 0.001
8	C, A, S ^h	205.7	4	< 0.001
9	CS, CAS ⁱ	9.4	2	< 0.01
10	CA, CS, CAS ^j	7.4	1	< 0.01

^a Derived from the illustrative data of table 1.

^b C = Cancer/compeer case, A = asbestos fibers present/absent in the lungs, S = smoking habits (smoker/nonsmoker).

^c Each model contains the configurations (terms) which are hypothesized as necessary in order to obtain the maximum likelihood estimates which fit the observed data well. The main effect terms C, A, and S and the general mean are included in each model. For example, the configuration CA includes the observed counts in the table which relates lung cancer to asbestos fibers in the lungs.

^d The degrees of freedom associated with each effect depend on the number of categories in the relevant variables.

^e Maximum difference between observed and fitted marginal totals was 0.1.

^f Saturated model (ie, fully parametrized).

^g Hierarchical, multiplicative type model.

^h Minimal model (ie, main effects only).

ⁱ Nonhierarchical, smoking-synergistic model.

^j Nonhierarchical, three-factor interaction model.

smoking interaction effect, and CAS = caseness-asbestos-smoking interaction effect. Thus each main or interaction effect is represented by a term in the log-linear model.

An array of models is developed that exhausts the possible hypotheses of causal relations among the variables (table 4). Given each hypothesis, the expected distribution of the data is tested for goodness-of-fit with the "observed" distribution of the data (table 1) with a chi-square distributed statistic (-2 times), the maximized log-likelihood ratio (termed deviance and represented symbolically by G²). A comparison of two models, one which includes the interaction (or effect) under investigation and one which does not, allows the contribution of the study variable to be tested.

Our primary interest in testing the departure from the additivity of effects was whether the multiplicative type of model (model 2 in table 4), which contained the associations of both asbestos

and smoking with lung cancer, would provide an accurate description of the data. For completeness all hierarchical models were fitted to the data. A hierarchical model may be described in terms of the marginal totals to be fit. Additional nonhierarchical models were tried in order to test the tenability of the possibility that the three-factor interaction lung cancer-asbestos-smoking (comparison of model 6 with 9 and model 10 with 2 in table 4) would be necessary to describe the distribution of numbers in each cell of the contingency (table 1). This action is equivalent to hypothesizing that in the presence of asbestos fibers the risk of lung cancer is raised more for smokers than for non-smokers. Or conversely that smoking has a greater effect, in terms of increase in lung cancer incidence, among persons with than without asbestos fibers in their lungs.

The results of the analysis of deviance are shown in table 4. Only the multiplicative type of hierarchical model 1 provided a good fit to the data. In fact this model

Table 5. Deviance statistics for interactions between lung cancer, asbestos fibers in the lungs, and smoking habits.

Interaction ^a (Difference ^b)	G ²	Degrees of freedom	p-value
CA (4—1)	17.1	1	< 0.001
CS (3—1)	150.6	1	< 0.001
AS (2—1)	7.8	1	< 0.01
CAS (1—0) ^c	0.2	1	NS
CAS (9—6) ^c	30.7	1	< 0.001
CAS (10—2) ^c	0.6	1	NS

^a C = Cancer/compeer case, A = asbestos fibers present/absent in the lungs, S = smoking habits (smoker/nonsmoker).

^b Each G² statistics of interaction was calculated from the difference of two deviance measures, each of which measured the goodness-of-fit of one of the two models being compared. The models used in the calculations of the G² statistics of interaction are enclosed in parentheses; the reference model giving a satisfactory fit.

^c The log-likelihood G² statistics for this interaction does not include the G² statistic, eg, for the association CA between lung cancer and asbestos fibers in the lungs.

matched the data very well; the deviance statistic was considerably smaller than its expected value (the degrees of freedom). Model 1 used seven parameters to describe eight cells (in table 1). Furthermore, the analysis showed that neither the entertained simpler of the two multiplicative hierarchical models (model 2) nor the non-hierarchical smoking-synergistic model (model 9) fitted the data satisfactorily enough. All the other tried models fitted the constructed data even less.

In searching for the most parsimonious hierarchical model, we adopted two strategies, namely, the forward selection and backward elimination procedures (1). Both approaches terminated in model 1, which includes the associations between lung cancer and smoking habits, between lung cancer and asbestos fibers, and the covariation between smoking and asbestos, when a strict acceptance or removal probability of 5 % for the model terms was adhered to. By inspecting the difference of the deviance statistics in table 4, we find the significance of the individual model components (table 5). In the assessment of significance, reference was made to the acceptable model 1. The positive association between lung cancer and asbestos fibers (CA) would again be highly significant. It is also seen from table 5 that the measured three-factor interaction term (CAS), in a multiplicative sense, between

lung cancer, asbestos fibers, and smoking habits would be needed in an attempt to describe the data adequately with the smoking-synergistic model (which suppresses the term CA), but it would be abundant for model 10.

We proceeded to calculate estimates for the frequencies in table 1. These fitted values, obtained from the application of model 1, are given in table 6. A comparison of tables 1 and 6 shows that the log-linear analysis yielded like results with the stratified analysis as far as the rate (ratio) calculations are concerned. To check that the values correspond to a multiplicative type of model, we multiplied the RRs of smoking and asbestos ($7.8 \times 1.95 = 15.2$), which nearly equals the RR of their combined effect (14.7). For the odds ratios the result is exact.

Discussion

The new versatile log-linear modeling technique gave results concordant with the stratified analysis. Furthermore, the analysis of deviance revealed that one of the entertained models would match the illustrative data agreeably. This particular model assumed a multiplicative type of action for the effects of the study variables, smoking and asbestos (terms CA and CS) and, in addition, a covariation (term AS) between them. Thus this model would

Table 6. Estimated frequencies, obtained from the fitting of a multiplicative type of model ^a to the data of table 1, and rate estimates.

	Asbestos fibers present		Asbestos fibers absent		Total
	Smokers	Non-smokers	Smokers	Non-smokers	
Lung cancer cases	371.1	28.9	88.9	11.1	500
Compeer cases	198.9	121.1	91.1	88.9	500
Estimate of the exposure category specific rate	2.94 %	0.39 %	1.56 %	0.20 %	
Estimate of rate ratio	14.7	1.95	7.8	1.0	

^a Model 1 of table 4.

state that asbestos and smoking are independently capable of producing lung cancer, but with constant RRs in each category of the other factor, and that the finding of asbestos fibers in the lungs and smoking history were (noncausally) linked in these data.

Greenland (3) has cautioned against an uncritical use of log-linear (or logistic) models for the multivariate analysis of epidemiologic data. His criticism was pointed at "exclusive use of one particular model" when additivity holds, since as "log-linear models imply a multiplicative statistical relationship between the effects of the study exposures," it can lead to interpretational difficulties.

We have attempted to clarify these interpretational pitfalls by supplementing the log-linear analysis with the analysis by RR employing, among others, the relative excess risk parameter. This dual approach is desirable as the quantitated relationship seldom conforms perfectly to either a multiplicative model or to an additive one. Moreover, the chosen model yielded cell estimates that were more stable than the "observed" three-way table frequencies, and these fitted estimates allowed us to quantitate the effects of the study variables and interactions between them in terms of exposure-specific rates and RRs. In the oversimplified case of the imaginary data, it was easy to test all the possible hierarchical models and also the previously advocated nonhierarchical ones. Thus, the danger of "the inadvertent ex-

clusion from consideration of other, possibly more appropriate models for disease risk [3]" was small. In a more complicated real-life situation with multiple continuous and discrete variables (both matched and unmatched), a number of strategies can be chosen for the statistical problem of model selection [such as those discussed by Benedetti & Brown (1)].

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