

Nonparametric evaluation of birth cohort trends in disease rates

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Background Although interpretation of age-period-cohort analyses is complicated by the non-identifiability of maximum likelihood estimates, changes in the slope of the birth-cohort effect curve are identifiable and have potential aetiological significance.

Methods A nonparametric test for a change in the slope of the birth-cohort trend has been developed. The test is a generalisation of the sign test and is based on permutational distributions. A method for identifying interactions between age and calendar-period effects is also presented.

Results The nonparametric method is shown to be powerful in detecting changes in the slope of the birth-cohort trend, although its power can be reduced considerably by calendar-period patterns of risk. The

method identifies a previously unidentified decrease in the birth-cohort risk of lung-cancer mortality from 1912 to 1919, which appears to reflect a reduction in the initiation of smoking by young men at the beginning of the Great Depression (1930s). The method also detects an interaction between age and calendar period in leukemia mortality rates, reflecting the better response of children to chemotherapy.

Conclusion The proposed nonparametric method provides a data analytic approach, which is a useful adjunct to log-linear Poisson analysis of age-period-cohort models, either in the initial model building stage, or in the final interpretation stage.

Keywords age-period-cohort model, nonparametric analysis, permutational test, lung cancer, leukemia.

Introduction

We have previously demonstrated that, in spite of the lack of unique estimates in general for the parameters specifying a particular age-period-cohort model, a change in the slope of the long-term linear trend in calendar-period effects, or in birth-cohort effects, can be identified unequivocally¹. Parametric methods were developed to identify changes in trends in birth-cohort or calendar-period parameters and it was demonstrated that such changes can have important implications regarding disease aetiology¹. Conventional age-period-cohort analyses of variation of disease rates over time assume a log-linear relationship of age, calendar-period and birth-cohort effects, and estimate the parameters specifying the model by Poisson maximum likelihood methods²⁻⁶. The log-linear relationship is suspect for some cancer mortality analyses, because there are known age-treatment interactions for some cancers (e.g. tamoxifen increases survival to a greater extent in post-menopausal than in pre-menopausal breast-cancer patients⁷) and there may be differences among age groups in the extent of excess risk imparted

by certain risk factors (e.g. childbearing history may have a greater impact on post-menopausal than pre-menopausal breast-cancer risk⁸). Methods for detecting changes in long-term trends that do not rely on the usual parametric assumptions underlying age-period-cohort analyses would therefore be useful. In addition, differences among age groups in the magnitude or direction of their calendar period trends can, in conventional analyses, lead incorrectly to indications of significant birth-cohort trends. Hence, methods for examining data for birth-cohort trends should be able to distinguish between such age-calendar-period interactions and a *bona fide* change in the magnitude or direction of the birth-cohort trend.

We present a nonparametric method to assist in the evaluation of trends in disease risk with birth cohort, or calendar period. The method, which requires no formal model specification, is based on permutational distributions and can identify changes in the slope of the linear trend in risk with successive birth cohorts (or calendar periods), as well as identify situations in which apparent birth-cohort trends can be explained by age acting as an

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effect-modifier of the calendar-period trend. A related technique has previously been applied to the analysis of trends in US Caucasian female breast-cancer mortality rates^{9,10}, and the results of the nonparametric approach have been verified using a parametric analysis¹. In this paper we present the development of a more powerful nonparametric method in detail. We examine the operating characteristics of the proposed permutation tests in a simulation study, verify the adequacy of normal approximations to the distribution of the proposed test statistic and illustrate the use of the technique in two examples, yielding very different interpretations of apparent birth-cohort trends.

Concepts and notation

The starting point for the nonparametric age-period-cohort analysis is, as with the corresponding parametric analysis, an array of disease rates classified by age interval and calendar period. Let $R_{i,j,k}$ denote the rate for the i th of A age intervals in the j th of P calendar year periods, where $k = A + j - i$ indexes the corresponding birth cohort. In this notation, there are $C = A + P - 1$ birth cohorts, with larger values of k corresponding to more recent birth cohorts. The standard parametric age-period-cohort analysis is based on Poisson regression with the log-linear model:

$$\log[E(R_{i,j,k})] = \alpha_i + \pi_j + \gamma_k \quad (1)$$

where the α_i are the age effects, the π_j are the calendar period effects and the γ_k are the birth-cohort effects.

Disease rates typically vary considerably with age, therefore the nonparametric procedure will be based on comparisons of age-specific rates. The first step in the nonparametric method is to determine within each age interval the directions of the changes in age-specific rates for all pairs of adjacent calendar periods. Accordingly, define the indicator variable $N_{i,r,s}$ to equal one if $R_{i,r+1,s+1} < R_{i,r,s}$ and to take the value zero if $R_{i,r+1,s+1} > R_{i,r,s}$, for $i = 1, 2, \dots, A$, $r = 1, 2, \dots, P-1$, and $s = 1, 2, \dots, C-1$. Thus, $N_{i,r,s} = 1$ indicates that the rate in age interval i was lower in period $r + 1$ than in period r (or, equivalently, lower in birth cohort $s + 1$ than in birth cohort s).

Before proceeding with the development of the method, consider an instructive example to introduce basic concepts of the nonparametric approach. Suppose there are five calendar periods and nine age groups, resulting in 13 birth cohorts. Table 1 shows what a tabulation of the indicator variables, $N_{i,r,s}$, would look like, with rows corresponding to age groups (i.e. to index i) and columns corresponding to the calendar periods being compared (i.e. to index r , where r indicates the comparison of period $r + 1$ to period r). Note that,

although there are five calendar periods and 13 birth cohorts in the example, there are only four paired comparisons of adjacent calendar periods and only 12 paired comparisons of adjacent birth cohorts.

Examination of patterns of change in adjacent birth cohorts is difficult in a tabulation like that shown in Table 1, because comparisons between the same two adjacent cohorts appear on downward diagonal rows. Thus, when examining cohort patterns it is useful to rearrange the table, so that all comparisons between the same two adjacent cohorts lie on the same horizontal row. Table 2 gives such a rearrangement of Table 1. In Table 2, each upward diagonal row corresponds to one of the nine age groups and each horizontal row contains all possible comparisons of age specific rates between the two adjacent birth cohorts listed on the left. From

Table 1 Tabulation of the indicator variables, $N_{i,r,s}$, for an example with five calendar periods and nine age groups

| Calendar periods compared | | | | |
|---------------------------|-------------|--------------|--------------|--------------|
| Age group | 2 to 1 | 3 to 2 | 4 to 3 | 5 to 4 |
| 1 | $N_{1,1,9}$ | $N_{1,2,10}$ | $N_{1,3,11}$ | $N_{1,4,12}$ |
| 2 | $N_{2,1,8}$ | $N_{2,2,9}$ | $N_{2,3,10}$ | $N_{2,4,11}$ |
| 3 | $N_{3,1,7}$ | $N_{3,2,8}$ | $N_{3,3,9}$ | $N_{3,4,10}$ |
| 4 | $N_{4,1,6}$ | $N_{4,2,7}$ | $N_{4,3,8}$ | $N_{4,4,9}$ |
| 5 | $N_{5,1,5}$ | $N_{5,2,6}$ | $N_{5,3,7}$ | $N_{5,4,8}$ |
| 6 | $N_{6,1,4}$ | $N_{6,2,5}$ | $N_{6,3,6}$ | $N_{6,4,7}$ |
| 7 | $N_{7,1,3}$ | $N_{7,2,4}$ | $N_{7,3,5}$ | $N_{7,4,6}$ |
| 8 | $N_{8,1,2}$ | $N_{8,2,3}$ | $N_{8,3,4}$ | $N_{8,4,5}$ |
| 9 | $N_{9,1,1}$ | $N_{9,2,2}$ | $N_{9,3,3}$ | $N_{9,4,4}$ |

Table 2 Cohort-period-change matrix with five calendar periods and nine age groups

| Calendar periods compared | | | | |
|---------------------------|-------------|--------------|--------------|--------------|
| Cohorts compared | 2 to 1 | 3 to 2 | 4 to 3 | 5 to 4 |
| 13 to 12 | | | | $N_{1,4,12}$ |
| 12 to 11 | | | $N_{1,3,11}$ | $N_{2,4,11}$ |
| 11 to 10 | | $N_{1,2,10}$ | $N_{2,3,10}$ | $N_{3,4,10}$ |
| 10 to 9 | $N_{1,1,9}$ | $N_{2,2,9}$ | $N_{3,3,9}$ | $N_{4,4,9}$ |
| 9 to 8 | $N_{2,1,8}$ | $N_{3,2,8}$ | $N_{4,3,8}$ | $N_{5,4,8}$ |
| 8 to 7 | $N_{3,1,7}$ | $N_{4,2,7}$ | $N_{5,3,7}$ | $N_{6,4,7}$ |
| 7 to 6 | $N_{4,1,6}$ | $N_{5,2,6}$ | $N_{6,3,6}$ | $N_{7,4,6}$ |
| 6 to 5 | $N_{5,1,5}$ | $N_{6,2,5}$ | $N_{7,3,5}$ | $N_{8,4,5}$ |
| 5 to 4 | $N_{6,1,4}$ | $N_{7,2,4}$ | $N_{8,3,4}$ | $N_{9,4,4}$ |
| 4 to 3 | $N_{7,1,3}$ | $N_{8,2,3}$ | $N_{9,3,3}$ | |
| 3 to 2 | $N_{8,1,2}$ | $N_{9,2,2}$ | | |
| 2 to 1 | $N_{9,1,1}$ | | | |

the definition of the $N_{i,r,s}$ values it follows that if the risk of disease decreased in the later birth cohort (i.e. indexed by $s+1$) compared with the earlier birth cohort (i.e. indexed by s) then the entries on row s of Table 2 will predominantly have value one. If the disease risk increased in the later birth cohort, on the other hand, the entries on row s will be predominantly zeros. The tabulation of the $N_{i,r,s}$ values arranged as in Table 2 will be referred to as the cohort-period-change matrix.

The pattern of zeros and ones in a cohort-period-change matrix can be very informative, as the following examples demonstrate. The data in Table 3 are constructed to indicate the pattern expected if there is a change in the slope of the birth-cohort trend in risk. In this contrived data-set, all age-specific rates increased 5% with each successive birth cohort, going from Cohort 1 through 7 and then all age-specific rates decreased 5% with each successive birth cohort, going from Cohort 7 through 13. Table 4 gives the cohort-period-change matrix for the contrived data in Table 3. The one in the top entry of the last column of Table 4 indicates a decrease in the youngest age group in going from Period 4 to 5 (i.e. from 1.7 to 1.6 per 100 000). Similarly, the zero in the bottom entry in the last column indicates an increase in the oldest age group in going from Period 4 to 5 (i.e. from 607.5 to 637.9 per 100 000). Although the change in the direction of disease risk indicated in Table 3 is more abrupt than would usually be expected, Table 4 is a useful paradigm to indicate the type of pattern created by changes in birth-cohort trends. In particular, note the difference in the distribution of zeros and ones in different blocks of successive horizontal rows of the cohort-period-change matrix. A decreasing birth-cohort trend over several successive birth cohorts creates a block of adjacent rows in which ones predominate, while an increasing birth-cohort trend over several successive cohorts creates a block of adjacent rows in which zeros predominate.

Table 3 Contrived disease rates (per 100 000) with increasing birth cohort trend from Cohort 1 to Cohort 7 and decreasing birth cohort trend from Cohort 7 to Cohort 13

| Age group | Calendar periods | | | | |
|-----------|------------------|-------|-------|-------|-------|
| | 1 | 2 | 3 | 4 | 5 |
| 1 | 2.0 | 1.9 | 1.8 | 1.7 | 1.6 |
| 2 | 4.1 | 3.9 | 3.7 | 3.5 | 3.3 |
| 3 | 8.2 | 7.8 | 7.4 | 7.0 | 6.7 |
| 4 | 16.4 | 17.2 | 16.4 | 15.5 | 14.8 |
| 5 | 32.8 | 34.4 | 36.2 | 34.4 | 32.6 |
| 6 | 65.6 | 68.9 | 72.3 | 75.9 | 72.1 |
| 7 | 131.2 | 137.8 | 144.6 | 151.9 | 159.5 |
| 8 | 262.4 | 275.5 | 289.3 | 303.8 | 318.9 |
| 9 | 524.8 | 551.0 | 578.6 | 607.5 | 637.9 |

It is clear, by analogy, that a change in the direction of the calendar period trend would result in a different distribution of zeros and ones in different blocks of adjacent columns of the cohort-period-change matrix. Thus, changes in cohort trends and changes in calendar period trends create very different patterns in the cohort-period-change matrix. A third situation is demonstrated in Table 5. Table 5 looks similar to Table 4, with a different distribution of ones in the top half of the table compared with the bottom half of the table. Table 5, however, corresponds to a situation in which disease rates are decreasing with calendar period in the three youngest age groups (i.e. all entries are ones in the top three diagonal rows), are increasing with calendar

Table 4 Cohort-period-change matrix for the contrived rate structure in Table 3, illustrating the paradigm for an abrupt change in the direction of the birth cohort trend

| Cohorts compared | Calendar periods compared | | | |
|------------------|---------------------------|--------|--------|--------|
| | 2 to 1 | 3 to 2 | 4 to 3 | 5 to 4 |
| 13 to 12 | | | | 1 |
| 12 to 11 | | | 1 | 1 |
| 11 to 10 | | 1 | 1 | 1 |
| 10 to 9 | 1 | 1 | 1 | 1 |
| 9 to 8 | 1 | 1 | 1 | 1 |
| 8 to 7 | 1 | 1 | 1 | 1 |
| 7 to 6 | 0 | 0 | 0 | 0 |
| 6 to 5 | 0 | 0 | 0 | 0 |
| 5 to 4 | 0 | 0 | 0 | 0 |
| 4 to 3 | 0 | 0 | 0 | |
| 3 to 2 | 0 | 0 | | |
| 2 to 1 | 0 | | | |

Table 5 Cohort-period-change illustrating heterogeneity of calendar period trends by age

| Cohorts compared | Calendar periods compared | | | |
|------------------|---------------------------|--------|--------|--------|
| | 2 to 1 | 3 to 2 | 4 to 3 | 5 to 4 |
| 13 to 12 | | | | 1 |
| 12 to 11 | | | 1 | 1 |
| 11 to 10 | | 1 | 1 | 1 |
| 10 to 9 | 1 | 1 | 1 | 1 |
| 9 to 8 | 1 | 1 | 0 | 0 |
| 8 to 7 | 1 | 1 | 0 | 1 |
| 7 to 6 | 0 | 0 | 1 | 0 |
| 6 to 5 | 1 | 1 | 0 | 0 |
| 5 to 4 | 0 | 0 | 0 | 0 |
| 4 to 3 | 0 | 0 | 0 | |
| 3 to 2 | 0 | 0 | | |
| 2 to 1 | 0 | | | |

period in the three oldest age groups (i.e. all entries are zeros in the bottom three diagonal rows) and are unchanged in the middle three age groups (i.e. 50% of the shaded entries are ones). In developing our method we want to be able to distinguish between such a heterogeneity of calendar period trends by age and a *bona fide* change in the birth-cohort trend.

Table 6 gives US lung cancer mortality rates for Caucasian males between the ages of 24 and 83 from 1970 to 1989. Table 7 presents the cohort-period-change matrix for the lung cancer data in Table 6. Summing across each horizontal row in Table 7 provides a summary comparison of the two birth cohorts listed in the first column. Each row sum, given in the last column of

Table 6 Two-year age and calendar year US male lung cancer mortality rates^a

| Age | Calendar period | | | | | | | | | |
|-------|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | 70-71 | 72-73 | 74-75 | 76-77 | 78-79 | 80-81 | 82-83 | 84-85 | 86-87 | 88-89 |
| 24-25 | 0.30 | 0.32 | 0.17 | 0.24 | 0.12 | 0.13 | 0.163 | 0.162 | 0.18 | 0.099 |
| 26-27 | 0.49 | 0.20 | 0.23 | 0.19 | 0.40 | 0.22 | 0.24 | 0.23 | 0.21 | 0.17 |
| 28-29 | 0.66 | 0.43 | 0.56 | 0.55 | 0.35 | 0.44 | 0.39 | 0.51 | 0.50 | 0.33 |
| 30-31 | 1.1 | 0.90 | 1.1 | 0.73 | 0.71 | 0.54 | 0.66 | 0.56 | 0.85 | 0.67 |
| 32-33 | 2.5 | 1.91 | 1.94 | 1.6 | 1.5 | 1.3 | 1.15 | 1.07 | 1.3 | 1.2 |
| 34-35 | 3.7 | 3.54 | 3.46 | 3.49 | 2.6 | 2.3 | 2.0 | 1.8 | 1.9 | 2.0 |
| 36-37 | 6.1 | 6.8 | 5.0 | 5.2 | 4.31 | 4.27 | 4.0 | 3.6 | 2.93 | 2.89 |
| 38-39 | 10.0 | 10.1 | 9.4 | 9.0 | 7.6 | 8.4 | 7.0 | 6.0 | 5.2 | 5.5 |
| 40-41 | 15.3 | 14.7 | 13.9 | 13.2 | 12.5 | 12.9 | 11.0 | 10.3 | 9.2 | 9.5 |
| 42-43 | 23.2 | 20.9 | 21.1 | 20.4 | 19.0 | 17.5 | 15.5 | 16.5 | 15.0 | 12.4 |
| 44-45 | 29.1 | 32.8 | 30.9 | 29.3 | 27.7 | 27.5 | 26.5 | 23.7 | 23.4 | 21.1 |
| 46-47 | 42.4 | 43.2 | 43.8 | 40.9 | 41.4 | 39.7 | 37.9 | 35.6 | 34.5 | 33.2 |
| 48-49 | 53.6 | 56.7 | 59.9 | 60.4 | 57.2 | 57.8 | 53.6 | 53.2 | 49.6 | 45.1 |
| 50-51 | 69.8 | 70.5 | 75.1 | 76.3 | 79.4 | 77.9 | 70.8 | 70.2 | 70.0 | 66.4 |
| 52-53 | 85.8 | 88.3 | 93.3 | 97.3 | 99.6 | 99.4 | 98.8 | 94.7 | 91.9 | 89.2 |
| 54-55 | 112.7 | 112.2 | 118.5 | 120.2 | 124.7 | 127.5 | 126.2 | 122.7 | 121.8 | 113.8 |
| 56-57 | 145.8 | 144.8 | 140.4 | 148.6 | 150.5 | 157.2 | 155.4 | 158.9 | 154.3 | 148.2 |
| 58-59 | 169.1 | 174.6 | 178.0 | 174.7 | 184.4 | 185.9 | 190.6 | 196.3 | 195.5 | 198.4 |
| 60-61 | 198.2 | 209.3 | 218.8 | 214.6 | 221.7 | 222.9 | 226.9 | 226.9 | 232.6 | 236.5 |
| 62-63 | 235.1 | 247.6 | 254.7 | 261.0 | 265.0 | 259.4 | 260.5 | 270.9 | 278.9 | 277.9 |
| 64-65 | 275.6 | 283.3 | 290.7 | 298.9 | 309.4 | 308.6 | 304.4 | 310.8 | 322.3 | 317.4 |
| 66-67 | 309.4 | 313.4 | 323.2 | 331.9 | 346.8 | 350.5 | 350.1 | 353.2 | 350.4 | 358.8 |
| 68-69 | 327.1 | 347.7 | 358.3 | 376.6 | 378.9 | 393.8 | 406.9 | 402.9 | 390.9 | 394.1 |
| 70-71 | 347.3 | 368.7 | 380.1 | 402.7 | 424.3 | 429.8 | 442.3 | 453.4 | 449.5 | 448.0 |
| 72-73 | 354.5 | 403.1 | 408.6 | 434.1 | 442.8 | 468.9 | 468.6 | 479.5 | 492.1 | 490.2 |
| 74-75 | 378.3 | 391.1 | 421.1 | 437.9 | 467.5 | 487.2 | 511.7 | 507.2 | 528.6 | 532.0 |
| 76-77 | 370.4 | 401.7 | 419.8 | 463.4 | 464.6 | 507.2 | 523.5 | 540.2 | 543.1 | 542.2 |
| 78-79 | 352.3 | 398.1 | 429.0 | 473.0 | 476.1 | 501.5 | 532.4 | 549.2 | 560.7 | 562.2 |
| 80-81 | 331.9 | 368.5 | 412.9 | 443.3 | 472.5 | 484.4 | 515.2 | 539.8 | 561.9 | 574.7 |
| 82-83 | 303.5 | 334.4 | 377.7 | 415.2 | 459.6 | 473.1 | 510.4 | 522.0 | 569.5 | 584.3 |

^aDeaths per 100 000 men.

Table 7 Cohort-period change matrix for two-year data on Caucasian male lung-cancer mortality in the USA

| Birth cohorts compared | Calendar periods compared | | | | | | | | | Sum |
|------------------------|---------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|-----|
| | 72-3 to 70-1 | 74-5 to 72-3 | 76-7 to 74-5 | 78-9 to 76-7 | 80-1 to 78-9 | 82-3 to 80-1 | 84-5 to 82-3 | 86-7 to 84-5 | 88-9 to 86-7 | |
| 1963 to 1961 | | | | | | | | | 1 | 1 |
| 1961 to 1959 | | | | | | | | 0 | 1 | 1 |
| 1959 to 1957 | | | | | | | 1 | 1 | 1 | 3 |
| 1957 to 1955 | | | | | | 0 | 0 | 1 | 1 | 3 |
| 1955 to 1953 | | | | | 0 | 0 | 0 | 0 | 1 | 1 |
| 1953 to 1951 | | | | 1 | 1 | 1 | 1 | 0 | 0 | 4 |
| 1951 to 1949 | | | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 |
| 1949 to 1947 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7 |
| 1947 to 1945 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |
| 1945 to 1943 | | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| 1943 to 1941 | | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| 1941 to 1939 | | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 5 |
| 1939 to 1937 | | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 6 |
| 1937 to 1935 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| 1935 to 1933 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| 1933 to 1931 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| 1931 to 1929 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 6 |
| 1929 to 1927 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 8 |
| 1927 to 1925 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 3 |
| 1925 to 1923 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 2 |
| 1923 to 1921 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 |
| 1921 to 1919 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1919 to 1917 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| 1917 to 1915 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 7 |
| 1915 to 1913 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 7 |
| 1913 to 1911 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1911 to 1909 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| 1909 to 1907 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 2 |
| 1907 to 1905 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1905 to 1903 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1903 to 1901 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 |
| 1901 to 1899 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | 0 |
| 1899 to 1897 | 0 | 0 | 0 | 0 | 0 | 0 | | | | 0 |
| 1897 to 1895 | 0 | 0 | 0 | 0 | 0 | | | | | 0 |
| 1895 to 1893 | 0 | 0 | 0 | 0 | | | | | | 0 |
| 1893 to 1891 | 0 | 0 | 0 | | | | | | | 0 |
| 1891 to 1889 | 0 | 0 | | | | | | | | 0 |
| 1889 to 1887 | 0 | | | | | | | | | 0 |

the table, yields the number of times age-specific rates were lower in the latter of the two cohorts listed in the first column. It is apparent in the lung cancer data that row sums tend to be large in the top half of Table 7, suggesting a decreasing cohort trend in recent cohorts, and small in the bottom half, suggesting an increasing cohort trend in early cohorts. To provide a useful nonparametric method, a technique is needed to quantify the degree to which such a pattern of row sums in a cohort-period-change matrix is unusual and, if the pattern is found to be unusual, to determine

if it is consistent with a change in the trend of birth-cohort risk.

Nonparametric test statistics

As noted above, changes in the birth-cohort trend will result in changes in the distribution of zeros and ones in the horizontal rows of the cohort-period-change matrix. Sums of the rows totals (the final column of Table 7) over consecutive rows in the table can quantify the direction of the birth-cohort trend. Consider blocks of seven consecutive rows, summarising the birth-cohort trend over a

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16-year period. The sum of the row totals for the upper shaded block of seven rows in Table 7 is 53, while the sum for the lower shaded block is 17. The difference between these two sums, 36, can be used to quantify the magnitude of the change in the direction of the birth-cohort trend in the latter era (1931-45) compared with the earlier era (1903-17). The shaded blocks in Table 7 were chosen to maximise this difference for blocks of seven rows. Two different permutation approaches have been examined to test the significance of this maximum difference, i.e. to test for a significant change in the birth-cohort trend in risk.

Method 1

The first approach is based on the permutation distribu-

tion within each age group, under the global null hypothesis that rates are constant over both calendar periods and birth cohorts. As noted earlier, comparisons of disease rates within age groups form the foundation of the nonparametric approach because age-specific rates will remain constant in the absence of any secular changes in disease risk. Thus, under the null hypothesis that disease rates are constant over both calendar years and birth cohorts, the distribution of the number of decreases in the n paired comparisons of age-specific disease rates, in adjacent calendar periods in a particular age group over $n + 1$ consecutive calendar periods, is the same as the distribution of the number of decreases in adjacent integers in all possible permutations of the integers one through $n + 1$. For example, the permuta-

Table 8 Exact distribution of number of decreases in consecutive integers in all permutations of the integers 1 to $n + 1$

| Number (n) of comparisons | Number of decreases | P |
|---------------------------|---------------------|-----------|
| 1 | 0 | 0.5000000 |
| | 1 | 0.5000000 |
| 2 | 0 | 0.1666667 |
| | 1 | 0.6666667 |
| | 2 | 0.1666667 |
| 3 | 0 | 0.0416667 |
| | 1 | 0.4583333 |
| | 2 | 0.4583333 |
| | 3 | 0.0416667 |
| 4 | 0 | 0.0083333 |
| | 1 | 0.2166667 |
| | 2 | 0.5500000 |
| | 3 | 0.2166667 |
| | 4 | 0.0083333 |
| 5 | 0 | 0.0013889 |
| | 1 | 0.0791667 |
| | 2 | 0.4194444 |
| | 3 | 0.4194444 |
| | 4 | 0.0791667 |
| | 5 | 0.0013899 |
| 6 | 0 | 0.0001984 |
| | 1 | 0.0238095 |
| | 2 | 0.2363095 |
| | 3 | 0.4793651 |
| | 4 | 0.2363095 |
| | 5 | 0.0238095 |
| | 6 | 0.0001984 |
| 7 | 0 | 0.0000248 |
| | 1 | 0.0061260 |
| | 2 | 0.1064732 |
| | 3 | 0.3873760 |
| | 4 | 0.3873760 |
| | 5 | 0.1064732 |

Table 8 Contd

| Number (n) of comparisons | Number of decreases | P |
|---------------------------|---------------------|-----------|
| 8 | 6 | 0.0061260 |
| | 7 | 0.0000248 |
| | 0 | 2.76E-06 |
| | 1 | 0.0013834 |
| | 2 | 0.0402557 |
| | 3 | 0.2431493 |
| | 4 | 0.4304178 |
| | 5 | 0.2431493 |
| | 6 | 0.0402557 |
| 7 | 0.0013834 | |
| 9 | 8 | 2.76E-06 |
| | 0 | 2.76E-07 |
| | 1 | 0.0002792 |
| | 2 | 0.0131834 |
| | 3 | 0.1254387 |
| | 4 | 0.3610984 |
| | 5 | 0.3610984 |
| | 6 | 0.1254387 |
| | 7 | 0.0131834 |
| 8 | 0.0002792 | |
| | 9 | 2.76E-07 |

tion (3, 2, 4, 5, 6, 8, 7, 1) has three decreases (3, 2; 8, 7; 7, 1) in adjacent integers. The probability distributions for n up to the value of nine are given in Table 8. The probability mass is heavily concentrated in the middle for all $n > 1$. Note, for example, that in the comparison over 10 time periods (i.e. $n = 9$), an observation of ≤ 2 decreases or ≥ 7 decreases (i.e. six of the 10 possible outcomes) would indicate a significant trend in disease rates using a two-sided test at the 5% nominal significance level. Examination of Table 7 reveals that age-specific rates increased significantly for all but one of the age intervals over 58 years of age, while rates decreased significantly for several age intervals under 46 years of age.

A permutational approach, to compare the difference between sums of consecutive row totals for two blocks of rows, can be based on these age-specific permutation distributions. In Table 7, for example, inferences can be based on the distribution obtained by generating 30 random permutations of the integers one through 10, each of the permutations corresponding to a particular age group. The distribution of the maximum difference between sums of row totals in Table 7 for disjoint blocks of size seven can be determined from the distribution generated by these 30 age-specific permutations, using Monte Carlo simulation. This approach assumes no calendar-period pattern, therefore it will be conservative. That is, if there are any calendar-period differences in risk, the variability among row sums will be smaller

than the variability under the global null hypothesis.

Suppose, for example, lung-cancer rates increased each calendar period from 1970 through 1977 and decreased each calendar period thereafter. If there is no birth-cohort pattern of risk (i.e. the null hypothesis for birth-cohort risk), the first three columns of Table 4 would contain predominantly zeros and the last six columns would contain predominantly ones. The row sums would show much less variability about their expected value of six than the row sums under the global null hypothesis would show about their expectation of 4.5. Thus, birth-cohort patterns could be obscured by strong calendar-period patterns. This is unlikely to pose a problem for analysis of cancer mortality rates at most sites and, for the lung cancer example in Table 7, the difference of 36 is highly significant ($p < 10^{-6}$) using this method.

Method 2

A second permutational approach makes inferences conditional on the observed calendar-period pattern of risk. Inference is based on a randomisation test generated by the distribution of all possible permutations of A ($A = 30$ in Table 7) upper diagonal rows (i.e. the rows corresponding to comparisons of age-specific rates in the same age interval). Based on a large number of randomly-selected permutations of the age-specific rows, the percentage of outcomes for which the maximum difference between sums of row totals for disjoint blocks of size

seven is ≥ 36 provides a Monte Carlo estimate of the permutational significance level. Based on one million random permutations, the difference of 36 in Table 7 is highly significant ($p = 8 \times 10^{-6}$).

Simulation study of permutation tests

A simulation study examined the operating characteristics of the two permutation approaches for age intervals and calendar periods identical to those in Table 7, using two age-distributions for disease rates (that for lung cancer among US men and that for breast cancer among US women). Poisson random variates were generated with means defined by the standard log-linear model described in equation (1)¹¹. As shown in Table 9, both methods performed adequately under the null hypothesis of no variation in risk with birth cohort (i.e. $\delta = 0$). The inflated error rate for the lung-cancer rates with $\delta = 0$ and the calendar-period trend defined by $\Delta = -0.1$ reflects the impact of ties due to zero counts at young ages (the breast-cancer rates are larger than lung-cancer rates at the younger age intervals). These lead to fewer decreases than expected in the top rows of the cohort-period-change matrix (corresponding to later birth cohorts).

In practice, age groups with multiple zero counts should be avoided in the application of the nonparamet-

ric methods. The results for $\delta = 0.01$ and $\Delta = 0$ indicate that the permutation approaches are remarkably powerful when there is no calendar-period pattern of risk. For $\delta = 0.01$ and $\Delta = 0$ the lung cancer rates in the oldest age group increase from 455 per 10^5 , in the first calendar period, to 498 per 10^5 , in the last calendar period. Rates in the youngest age group decrease from 2.1 per 10^6 , in the first calendar period, to 1.9 per 10^6 , in the last calendar period.

The conservative nature of Method 1 in the presence of a calendar-period pattern of risk is demonstrated by the low power when $\delta = 0.075$ and $\Delta = 0.1$. The power of the methods for the breast-cancer case with $\delta = 0.085$ and $\Delta = -0.1$ is remarkable. For this case, the birth-cohort trend is not strong enough to change the number of decreases expected, based on the calendar-period pattern in any age group. Rates decrease with each calendar period from Periods 1 through 6 and increase with each calendar period from Periods 6 through 10 for each age group. However, the pattern is such that the rate decreases are larger than the increases in younger age groups, while the rate increases are much larger than the decreases in older age groups, which leads to row sums sufficiently different to provide power in excess of 90% for both methods.

Table 9 Monte Carlo simulation results (the rejection frequency in 1000 random pseudo-samples) examining the false positive error rate and power of the permutation tests at a 5% nominal level

| Model | | Breast cancer rates | | Lung cancer rates | |
|---------------------|---------------------|---------------------|----------|-------------------|----------|
| Cohort ^a | Period ^b | Method 1 | Method 2 | Method 1 | Method 2 |
| 0 | 0 | 0.034 | 0.041 | 0.027 | 0.033 |
| 0 | 0.1 | 0.000 | 0.006 | 0.000 | 0.049 |
| 0 | -0.1 | 0.000 | 0.021 | 0.000 | 0.086 |
| 0.01 | 0 | 0.994 | 0.982 | 1.000 | 1.000 |
| 0.075 | 0.1 | 0.232 | 0.866 | 0.497 | 0.932 |
| 0.085 | 0.1 | 0.942 | 0.943 | 0.923 | 0.998 |
| 0.085 | -0.1 | 0.930 | 0.942 | 0.355 | 0.412 |

^aThe coefficient δ , where the birth-cohort parameters in the standard log-linear age-period-cohort model are defined by the equations:

$$\gamma_k = \delta(k - 1) \text{ for } k = 1, 2, \dots, 19 \text{ and } \gamma_k = \delta(39 - k) \text{ for } k = 20, 21, \dots, 39.$$

^bThe coefficient Δ , where the calendar period parameters in the standard log-linear age-period-cohort model are defined by the equations:

$$\pi_j = \Delta(j - 1) \text{ for } j = 1, 2, \dots, 6 \text{ and } \pi_j = \Delta(11 - j) \text{ for } j = 7, 8, 9, 10.$$

Normal approximation to method 1

For the age-specific permutation distributions underlying the first approach, it can be shown that for any n disease rate comparisons in the same age interval over $n + 1$ consecutive calendar periods, the expected number of decreases under the null hypothesis of equal rates over time is $n/2$ and the variance is $(n + 2)/12$ (see Appendix 1). Comparisons in different age intervals are independent and the number of decreases in any block of comparisons can be expressed as the sum of the numbers of decreases in sub-blocks, where each sub-block represents comparisons within the same age interval. Therefore, the mean and variance of any block of comparisons represented in the cohort-period-change matrix can be calculated by summing the means and variances of the component age-specific sub-blocks. For example, the number of decreases in a block of H consecutive birth cohorts compared over K consecutive calendar periods (restricted to blocks over which comparisons can be made over all K calendar periods) can be calculated as the sum of the number of decreases in $H + K - 3$ sub-blocks, each representing people in the same age interval. In each block of eight consecutive birth cohorts between 1903 and 1945, compared over the 10 calendar periods in Table 7, there are 15 such sub-blocks, each representing a 2-year age interval. There are two sub-blocks each with 1, 2, 3, 4, 5 and 6 comparisons, and three sub-blocks with 7 comparisons. It follows that for the 63 possible comparisons in such a block of consecutive birth cohorts, the mean number of decreases is calculated as:

$$2 \times (1+2+3+4+5+6)/2 + 3 \times 7/2 = 31.5$$

and the variance is calculated as:

$$2 \times (3+4+5+6+7+8)/12 + 3 \times 9/12 = 7.75$$

Similarly, it follows that for a block of five consecutive age intervals, compared over the 10 calendar periods in Table 2, the mean number of decreases is $5 \times 9/2 = 22.5$ and the variance is $5 \times 11/12 = 4.58$.

More generally, let R denote any block of cells in a cohort-period-change matrix, such as that in Table 7. The total number of decreases in the block can be calculated as $D_R = \sum_i \sum_r N_{i,r}$, where the summation is over the age intervals indexed by i and calendar periods indexed by r which define the block R . The total number of comparisons in block R can be calculated as $T_R = \sum_i \sum_r (N_{i,r} + M_{i,r})$ where $M_{i,r} = 1 - N_{i,r}$. The expected number of decreases in block R is $T_R/2$. The variance of the number of decreases is $V_R = \sum_i (n_i + 2)/12$ where n_i is the number of comparisons in the i th age interval in block R .

To test the null hypothesis of no change in mortality rates over time in block R , define the test statistic:

$$Z_R = (D_R - T_R/2 \pm 0.5) / \sqrt{V_R}$$

where the continuity correction, 0.5, is added when $D_R - T_R/2 \leq -0.5$ and is subtracted when $D_R - T_R/2 \geq 0.5$. The normal approximation, based on Z_R , was evaluated for a block of eight consecutive birth cohorts compared over 10 consecutive time periods in a Monte Carlo simulation study and found to be quite good (Table 10). For very small blocks, the exact distribution can be enumerated, or a Monte Carlo approximation of the exact distribution can be employed.

Let P_R denote the proportion of comparisons in block R indicating decreases, that is, $P_R = D_R/T_R$. Then, to compare the frequency of decreases in two disjoint blocks, R_1 and R_2 , in a cohort-period-change matrix the statistic:

$$Z_{R_1, R_2} = (P_{R_1} - P_{R_2}) / \sqrt{V_{R_1, R_2}}$$

where V_{R_1, R_2} , the variance of the difference in proportions, derived in Appendix 2, can be compared with the percentiles of a standard normal distribution. As with the test statistic, Z_R , if there are concerns about the adequacy of the normal approximation for small samples, Monte Carlo simulations can be performed to approximate the exact distribution.

The test statistics defined above can be used to investigate the presence of different birth-cohort trends. Evidence of variation in risk by birth cohort is obtained when two disjoint blocks of birth cohorts differ considerably in the number of decreases observed in comparisons made over the same calendar year interval. For example, Z_R may indicate a significant excess of decreases in one block of birth cohorts and a significant deficit of decreases in a second block of birth cohorts⁹. In general, the variation between blocks of birth cohorts will not be as dramatic as that observed in the breast-cancer example and the statistic Z_{R_1, R_2} will be a better statistic for routine evaluation of potential birth-cohort trends.

In order to avoid artifact differences, induced by changes in calendar-period trends, comparisons of disjoint blocks of row sums in the cohort-period-change matrix will be restricted to the $A - P + 1$ rows representing birth cohorts for which all $P - 1$ comparisons between adjacent calendar periods are possible (i.e. eliminating comparisons in the upper and lower triangle region comprising the first $P - 2$ and last $P - 2$ rows in a cohort-period-change matrix, such as Table 2). The upper and lower triangular regions of the cohort-period-change matrix must also be eliminated when evaluating changes in calendar-period trends based on comparisons of disjoint blocks of column sums.

Table 10 Comparison of approximate two-sided significance levels based on the uncorrected and continuity corrected test statistics, Z_R , for blocks of seven consecutive birth cohorts, compared over 10 consecutive calendar year periods

| Observed number of decreases ^a | Simulated probability ^b | Uncorrected statistic | Corrected statistic |
|---|------------------------------------|-----------------------|----------------------|
| 31 or 32 | 1.000 | 0.857 | 1.000 |
| 30 or 33 | 0.719 | 0.590 | 0.720 |
| 29 or 34 | 0.471 | 0.369 | 0.473 |
| 28 or 35 | 0.279 | 0.209 | 0.281 |
| 27 or 36 | 0.149 | 0.106 | 0.151 |
| 26 or 37 | 0.071 | 0.048 | 0.072 |
| 25 or 38 | 0.030 | 0.019 | 0.031 |
| 24 or 39 | 0.011 | 0.007 | 0.012 |
| 23 or 40 | 3.7×10^{-3} | 2.3×10^{-3} | 4.0×10^{-3} |
| 22 or 41 | 1.1×10^{-3} | 6.4×10^{-4} | 1.2×10^{-3} |
| 21 or 42 | 2.7×10^{-4} | 1.6×10^{-4} | 3.3×10^{-4} |

^aThe distribution is symmetric about the mean value of 31.5.

^bMonte Carlo estimate of the exact probability based on 5 000 000 randomly-generated pseudo-samples.

Test for interactions

Another use of the test statistic, Z_{R_1, R_2} is to investigate the presence of age–calendar–period interactions. As noted earlier, different trends in risk among different age groups can give the appearance of variation in risk among birth cohorts. To motivate the approach, consider the patterns in Tables 4 and 5. If there is a *bona fide* change in the birth-cohort trend, the situation represented in Table 4, there should be evidence of the change in every age group affected by the change in trend. Examination of comparisons within the middle age group in Table 4 (i.e. the middle three diagonal rows) indicates that all six of the table entries in or above the sixth horizontal row are ones, while all six of the table entries below the sixth horizontal row are zeros. That is, within any age group spanning a *bona fide* change in cohort trend, there should be evidence of that change in analysis restricted to that age group. In Table 5, however, the same analysis shows that 50% of the six shaded table entries in or above the sixth horizontal row are ones, as is the case for the six shaded entries below the sixth row. Thus, stratification by age eliminates the apparent evidence of a change in cohort trend.

Accordingly, the test statistic Z_{R_1, R_2} can be used to rule out an age–calendar–period trend interaction. Suppose significant differences have been found between disjoint blocks of birth cohorts and let R be the block providing strongest evidence of the trend change. Con-

sider the age blocks corresponding to different decades of age. For any such age block, denoted B, which intersects the block R of birth cohorts, determine the number of decreases in the age block among birth cohorts preceding R, among birth cohorts in R and among birth cohorts following R. The statistic Z_{R_1, R_2} can be used to test for differences within each age group between the comparisons within R and those preceding and/or following R. If the variation in rates is due to a change in the birth-cohort trend, the proportion of decreases in the intersection of blocks R and B should differ from the proportion in B among cohorts preceding or following R. If the proportions are homogeneous within age blocks and, moreover, there is evidence of heterogeneity among age blocks, then the variation in rates may be due to age–period interactions.

Issues related to block size

The size of the blocks of birth cohorts to use in the non-parametric analyses is an important consideration. If the chosen size of the blocks is too small, there may be problems with multiple comparisons; if the size is chosen too large, important trends may be obscured. Based on previous studies of breast cancer, blocks of eight birth cohorts were used in the previous application of the nonparametric method, to investigate trends in breast cancer among US Caucasian females during 1969–88⁹. Birth-cohort blocks of size eight provide a

reasonable compromise for comparisons over 30 age intervals and 10 calendar periods, so we will continue to use blocks of this size in the examples given below.

Our interest is in separating period trends from birth-cohort trends, we therefore restrict the initial comparison of birth-cohort blocks to those birth cohorts for which comparisons can be made over all 10 calendar periods. In Table 2 there are 16 such blocks of eight consecutive birth cohorts so a conservative Bonferroni adjustment for multiple comparisons using the statistic Z_R can be obtained by multiplying the p value for each block of cohorts by 16^{12} . Similarly, there are 45 possible comparisons of two disjoint blocks of eight birth cohorts among the 23 birth cohorts with comparisons over all 10 calendar periods, so a conservative multiple comparisons adjustment for $Z_{R1,R2}$ can be obtained by multiplying the observed p value by 45. If the number of age intervals is large, the Bonferroni adjustment may be extremely conservative, and, in such a situation, Monte Carlo simulations can be performed to better approximate the exact significance level of the observed difference.

Applications of approximate methods

US male lung cancer mortality rates, $R_{i,j,k}$, are given in Table 6 from 1970 to 1989 for ages 24-83. The corresponding cohort-period-change matrix is presented in Table 7. Examination of Table 7 reveals predominantly rate increases (i.e. zeroes) in the bottom of the matrix and predominantly rate decreases in the top of the matrix. Comparing the block of birth cohorts with the most decreases (i.e. 1931-45) with the block of cohorts with the fewest decreases (i.e. 1903-17) yields $Z_{R1,R2} =$

-9.017 ($p < 10^{-6}$). Using the conservative adjustment for multiple comparisons, any value of $Z_{R1,R2}$ exceeding 3.26 in absolute value is significant at the nominal 5% level. Thus, the lung-cancer data exhibit clear evidence of heterogeneity between birth cohorts.

Three 10-year age intervals intersect the 1931-45 block of birth cohorts (i.e. 30-39, 40-49, and 50-59 years of age). Among 30-39-year olds, there were 25 comparisons within the block of birth cohorts of which 72% gave decreases and 20 comparisons after the block of birth cohorts of which 70% gave decreases. Comparison of these percentages (Table 11) yields $Z_{R1,R2} = -0.18$ ($p = 0.86$). Thus, there is no evidence of heterogeneity in men born in cohorts after the 1931-45 block and among men born within the block. Among 40-49-year olds, there were 29 comparisons within the block of birth cohorts, of which 93% gave decreases, and 15 comparisons before the block of birth cohorts, of which 40% gave decreases. Comparing these percentages (Table 11) yields $Z_{R1,R3} = 4.33$ ($p = 1.5 \times 10^{-5}$). Among 50-59-year olds, there were six comparisons within the block of birth, all of which gave decreases, and 39 comparisons before the birth cohort, of which 41% gave decreases. Comparing these percentages (Table 11) gives $Z_{R1,R3} = 3.27$ ($p = 0.001$). Thus, within both the 40-49 and the 50-59-year age group, the change in trend in lung-cancer mortality rates appears to be a cohort presence, starting with men born in the late 1920s. The presence of highly significant birth cohort effects in lung-cancer mortality has been reported previously based on Poisson age-period-cohort modeling¹³ and our analysis suggests that the abrupt change in lung-cancer risk is predominantly a birth-cohort phenomenon and

Table 11 Analysis by decade of age for male lung cancer

| | | 10-year age groups | | |
|----------------------------------|------------------------------------|--------------------|--------|-------|
| | | 30-39 | 40-49 | 50-59 |
| Within the 1931-45 birth cohorts | Number of comparisons (T_{R1}) | 25 | 29 | 6 |
| | Number of decreases (D_{R1}) | 18 | 27 | 6 |
| | Variance (V_{R1}) | 2.917 | 3.25 | 1.00 |
| After the 1931-45 birth cohorts | Number of comparisons (T_{R2}) | 20 | | |
| | Number of decreases (D_{R2}) | 14 | | |
| | Variance (V_{R2}) | 2.500 | | |
| | | $Z_{R1,R2}$ | -0.178 | |
| Before the 1931-45 birth cohorts | Number of comparisons (T_{R3}) | | 15 | 39 |
| | Number of decreases (D_{R3}) | | 6 | 16 |
| | Variance (V_{R3}) | | 2.083 | 4.083 |
| | | $Z_{R1,R3}$ | 4.330 | 3.266 |

does not result from age–calendar–period interactions.

The apparent change in birth-cohort slope beginning around 1930 can be evaluated using the parametric contrasts given in Appendix 2 of an earlier paper¹ to compare the birth-cohort trend from 1903 through 1917 with the birth-cohort trend from 1931 through 1945. Substituting the maximum likelihood estimators for the γ 's based on Poisson regression analysis of the full age–period–cohort model using the lung-cancer data gives $C_1 = -0.614$ with an estimated standard error (SE) = 0.0254, and $C_2 = -7.147$ with an estimated SE = 0.226. Thus, both parametric contrasts provide strong evidence of the moderation of lung-cancer risk beginning with birth cohorts around 1930.

Although identification of short-term changes in trend is problematic, because of the multiplicity of possible comparisons in any cohort–period–change matrix, it is interesting that the lung-cancer birth-cohort trend turned negative from 1913–17, briefly interrupting a relentless increase in lung-cancer risk with successive birth cohorts. The sum of 14 for the 1913–15 and 1915–17 rows differs significantly from the sum of one observed for both the immediately preceding and following pairs of rows ($p = 3 \times 10^{-4}$ adjusted for the 190 possible comparisons of disjoint blocks of size two). Both permutational approaches indicate that a maximum difference of 13 would be significant for all comparisons of pairs of disjoint rows ($p = 10^{-4}$ for Method 1 and $p = 0.003$ for Method 2), so the observed decrease in birth-cohort risk from 1913–17 is highly unlikely to be due to chance.

Now consider leukemia mortality rates for US Caucasians from birth to age 69. Table 12 gives the cohort–period–change matrix for leukemia mortality. Although there is no dramatic difference between blocks of birth cohorts, the comparison of the block with the largest number of decreases (i.e. 1957–71) with the block with the fewest number of decreases (i.e. 1917–31) yields $Z_{R1,R2} = 3.43$.

There are 35 age groups in the leukemia example, resulting in 105 possible comparisons of disjoint blocks of eight consecutive birth cohorts, and use of the conservative multiple comparisons adjustment indicates only marginal significance ($p = 0.06$). Monte Carlo simulations reveal that the observed extreme difference between the blocks of birth cohorts is, in fact, significant ($p = 0.023$). Poisson regression analysis indicates significant birth-cohort effects ($p < 10^{-6}$, details not shown), suggesting the need for further investigation of the birth-cohort pattern of risk.

Three 10-year age groups intersect the 1957–71 block of birth cohorts (i.e. 0–9, 10–19 and 20–29 years of age). Among 0–9 year olds there were 15 comparisons within the 1957–71 block of birth cohorts, of

which 87% gave decreases, and there were 30 comparisons after the block of birth cohorts, of which 80% gave decreases. Comparison of these percentages (Table 13) gives $Z_{R1,R2} = 0.55$ ($p = 0.58$). Among 10–19 year olds there were 33 comparisons within the block of birth cohorts, of which 76% gave decreases, and six comparisons after the block, of which 83% gave decreases. Comparison of these percentages yields $Z_{R1,R2} = -0.41$ ($p = 0.68$). Similarly, comparison of percentages before the 1957–71 birth cohorts with those within the block of cohorts (Table 13) showed no significant difference for 10–19 year olds ($p = 0.62$) or for 20–29 year olds ($p = 1.0$). Thus, in none of the three age groups intersecting the 1957–71 birth cohorts is there any evidence of a change in trend with birth cohort. There is, however, evidence of heterogeneity among age groups. The percentages of decreases by decade of age are 82% for 0–9, 76% for 10–19, 60% for 20–29, 67% for 30–39, 60% for 40–49, 56% for 50–59 and 49% for 60–69. The difference in the percentages between the oldest and youngest decades of age is highly significant ($p < 10^{-6}$), so the apparent birth-cohort effects can be explained largely by age–calendar–period interactions.

Discussion

The nonparametric methods proposed above allow model-free inferences regarding changes in trends in disease rates with birth cohorts, or calendar periods. Although such second-order effects are customarily considered to be of secondary importance to first-order effects, they can, nonetheless, have important interpretations regarding disease aetiology¹. The nonparametric method can serve as a data analytic adjunct to the parametric, Poisson modeling methods, usually employed for age–period–cohort analyses, useful either in the model-building stage, or in the interpretation stage. As illustrated in the examples, the method can detect changes in the slope of trends in disease risk with birth cohort and provides a means for investigating age–calendar–period interactions. When inferences can be made using the nonparametric analysis, they have the advantage of being model-free.

There are situations in which the nonparametric method may have poor efficiency. In examples in which all age-specific disease rates show striking, monotone trends throughout the study period, the cohort–period–change matrix will consist of almost entirely zeros or ones (e.g. for stomach cancer mortality). This gives little variation in row sums (or column sums) of the cohort–period–change matrix. No calendar–period pattern of risk (excluding interactions) can induce the pattern of differences in the row sums of a cohort–period–change matrix, evaluated by the nonparametric method to test for changes in the birth-cohort trend.

Table 12 Cohort-period change matrix for two-year data on US white leukemia mortality

| Birth cohorts compared | Calendar periods compared | | | | | | | | | Sum |
|------------------------|---------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|-----|
| | 72-3 to 7-1 | 74-5 to 72-3 | 76-7 to 74-5 | 78-9 to 76-7 | 80-1 to 78-9 | 82-3 to 80-1 | 84-5 to 82-3 | 86-7 to 84-5 | 88-9 to 86-7 | |
| 1987 to 1985 | | | | | | | | | 0 | 0 |
| 1985 to 1983 | | | | | | | | 1 | 1 | 2 |
| 1983 to 1981 | | | | | | | 1 | 0 | 1 | 2 |
| 1981 to 1979 | | | | | | 0 | 1 | 0 | 1 | 2 |
| 1979 to 1977 | | | | | 1 | 0 | 1 | 1 | 1 | 4 |
| 1977 to 1975 | | | | 1 | 1 | 1 | 1 | 0 | 1 | 5 |
| 1975 to 1973 | | | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 6 |
| 1973 to 1971 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| 1971 to 1969 | | | | | | | | | | 7 |
| 1969 to 1967 | | | | | | | | | | 6 |
| 1967 to 1965 | | | | | | | | | | 8 |
| 1965 to 1963 | | | | | | | | | | 6 |
| 1963 to 1961 | | | | | | | | | | 7 |
| 1961 to 1959 | | | | | | | | | | 5 |
| 1959 to 1957 | | | | | | | | | | 8 |
| 1957 to 1955 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 5 |
| 1955 to 1953 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 6 |
| 1953 to 1951 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 4 |
| 1951 to 1949 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 |
| 1949 to 1947 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| 1947 to 1945 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 |
| 1945 to 1943 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7 |
| 1943 to 1941 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 7 |
| 1941 to 1939 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |
| 1939 to 1937 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| 1937 to 1935 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 5 |
| 1935 to 1933 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 6 |
| 1933 to 1931 | | | | | | | | | | 6 |
| 1931 to 1929 | | | | | | | | | | 5 |
| 1929 to 1927 | | | | | | | | | | 5 |
| 1927 to 1925 | | | | | | | | | | 4 |
| 1925 to 1923 | | | | | | | | | | 5 |
| 1923 to 1921 | | | | | | | | | | 4 |
| 1921 to 1919 | | | | | | | | | | 4 |
| 1919 to 1917 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 6 |
| 1917 to 1915 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | | 7 |
| 1915 to 1913 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | | | 3 |
| 1913 to 1911 | 0 | 1 | 0 | 1 | 0 | 0 | | | | 2 |
| 1911 to 1909 | 1 | 1 | 0 | 0 | 0 | | | | | 2 |
| 1909 to 1907 | 1 | 0 | 1 | 0 | | | | | | 2 |
| 1907 to 1905 | 1 | 1 | 0 | | | | | | | 2 |
| 1905 to 1903 | 0 | 1 | | | | | | | | 1 |
| 1903 to 1901 | 0 | | | | | | | | | 0 |

However, the efficiency of the nonparametric test for birth-cohort trends can be affected by the pattern of calendar-period risk. That is, in the presence of powerful calendar-period patterns of risk, birth-cohort trends in risk may not be detectable using the nonparametric approach. Birth-cohort patterns tend to be more dominant than calendar-period patterns in cancer research

and thus the nonparametric method has been useful in evaluating cancer trends. For example, the nonparametric method detected important birth-cohort trends in analyses of US breast-cancer mortality rates^{9,10}, in spite of strong and significant calendar-period trends in risk¹⁴. Nonetheless, the nonparametric approach has limitations and, for situations in which the log-linear modeling of

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Table 13 Analysis by decade of age for leukemia

| | | 10-year age groups | | |
|-------------------------------------|------------------------------------|--------------------|--------|-------|
| | | 0-9 | 10-19 | 20-29 |
| Within the 1957-71 birth cohorts | Number of comparisons (T_{R1}) | 15 | 33 | 15 |
| | Number of decreases (D_{R1}) | 13 | 25 | 9 |
| | Variance (V_{R1}) | 2.083 | 3.583 | 2.083 |
| After the 1957-71 birth cohorts | Number of comparisons (T_{R2}) | 30 | 6 | |
| | Number of decreases (D_{R2}) | 24 | 5 | |
| | Variance (V_{R2}) | 3.333 | 1 | |
| | $Z_{R1,R2}$ | 0.548 | -0.413 | |
| Before the 1957-71 birth cohorts | Number of comparisons (T_{R3}) | | 6 | 30 |
| | Number of decreases (D_{R3}) | | 4 | 18 |
| | Variance (V_{R3}) | | 1 | 3.333 |
| | $Z_{R1,R3}$ | | 0.496 | 0.000 |

age-period-cohort effects is appropriate, parametric evaluation of trends in birth cohorts or calendar periods using Poisson regression analysis, with appropriately chosen identifiable parameters, will provide a more powerful approach to detecting trend changes. Parametric methods should also be performed to verify and quantify changes in the slope of trends in disease risk identified by the nonparametric approach¹. Despite limitations, however, the nonparametric method developed in this paper can be a useful data-analytic tool in examining trends in disease risk.

Application of the nonparametric method to US male lung-cancer mortality rates demonstrated a striking moderation in risk, beginning with men born in the late 1920s. As Brown and Kessler have noted, this decrease in lung-cancer mortality can be explained by a downward trend in the prevalence of smoking in young men, which occurred as the adverse health effects of smoking became evident and were publicised¹³. The apparent brief decrease in the birth-cohort trend, indicated for men born 1913-17, probably resulted from an economically-induced decrease in the percentage of young men who began smoking during the early years of the Great Depression (1930s). Although the Depression had a marked impact on the trend of cigarette consumption¹⁵, the nonparametric analysis of lung-cancer presented in this paper is the first analysis to note any consequences of this reduced cigarette smoking on lung-cancer risk.

Application of the nonparametric method to US leukemia mortality-rates indicated that what appeared to

be a strong change in the slope of the birth-cohort trend could be explained largely by heterogeneity in mortality trends among different age groups. That is, mortality rates are decreasing more rapidly in patients < age 20 than in patients > 40. This disparity is due to recent advances in chemotherapy, which have resulted in greater improvements in prognosis for young leukemia patients than for older leukemia patients^{16,17}.

Appendix Age-specific permutation distributions underlying the first approach

For the age interval indexed by i , the number of decreases over $n + 1$ consecutive time-periods is given by $S_n = \sum_r N_{i,r}$ where the index corresponding to birth cohort has been suppressed and summation is over the n consecutive integers denoting the time-period comparisons under consideration. Under the null hypothesis, $E(N_{i,r}) = 1/2$ for all r , so that $E(S_n) = n/2$. The variance of S_n is given by:

$$v_n = \sum_r \text{variance}(N_{i,r}) + 2\sum_r \sum_{t>r} \text{covariance}(N_{i,r}, N_{i,t})$$

where the summations again are over the n consecutive integers denoting the relevant time periods. The variance of each $N_{i,r}$ is equal to $1/4$ and the covariance terms are all equal to zero, except in the $n-1$ cases in which $t = r + 1$. Under the permutational distribution, the product $N_{i,r} N_{i,r+1}$ takes the value one, with probability $1/6$ (of the six possible permutations of the integers 1, 2, and 3

only the outcome 3, 2, 1 results in two decreases), and the value zero, with probability 5/6. Thus, $E(N_{i,r}N_{i,r+1}) = 1/6$ and $\text{covariance}(N_{i,r}, N_{i,r+1}) = -1/12$. Thus,

$$v_n = n/4 - 2(n-1)/12 = (n+2)/12$$

Variance of the difference in proportions

In deriving the variance, $V_{R1,R2}$, for the difference in the proportion of decreases between two disjoint blocks of comparisons in the cohort-period-change matrix, that is, $P_{R1} - P_{R2} = D_{R1}/T_{R1} - D_{R2}/T_{R2}$, a covariance term enters in if the blocks have adjacent rows. This will always be the case, for as follows in applying the method to investigate age-calendar-period interactions. In such cases, $N_{i,r}$ will be included in one block and $N_{i,r+1}$ will be included in the other block for some i and some r . Letting U denote the number of such occurrences for $R1$ and $R2$, the variance of the difference, $P_{R1} - P_{R2}$, is given by:

$$V_{R1,R2} = V_{R1}/T_{R1}^2 + V_{R2}/T_{R2}^2 + U/(6T_{R1}T_{R2})$$

where V_R , the variance of D_R , has been derived in the text.

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