Mantel–Haenszel Analysis of Oxford Data. I. Independent Effects of Several Birth Factors Including Fetal Irradiation [1, 2]

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SUMMARY—Data from the Oxford Survey of Childhood Cancers were subjected to the Mantel–Haenszel procedures to recognize independent effects of associated factors in retrospective data. Our results showed that several birth factors, including fetal irradiation, social class, maternal age, and sibship position, exerted separate effects on childhood cancers in general, and reticuloendothelial system neoplasms in particular.—J Natl Cancer Inst 56: 879–883, 1976.

Maternal age and sibship position are examples of birth factors which not only influence the risk of obstetric radiography but also have associations with early death from leukemia (*1, 2*). Therefore, the uncertainty about whether to include fetal irradiation among the causes of childhood cancers could be due to the fact that we do not know how many of the following birth factors exert independent effects on these diseases: social class, maternal age, sibship position, and fetal irradiation. The Oxford Survey of Childhood Cancers has become an important source of information under these headings (*3*), and the purpose of this report is to show the effects of applying to these data the Mantel–Haenszel procedures for the identification of separate effects of associated factors in retrospective surveys (*4*).

MANTEL–HAENSZEL ANALYSIS OF RETROSPECTIVE DATA

A major problem with all retrospective surveys is the avoidance of spurious associations due to incorrect choice of statistical and data collection procedures for control of factors known or suspected of influencing the prevalence of human diseases. Deliberate matching of cases and controls is of limited value because only in relation to unmatched factors is there any possibility of detecting factors of etiologic importance. Nevertheless, some matching is essential if only to obtain case and control groups of comparable age and sex.

The remedy lies in deliberate matching of cases and controls for factors that can be easily studied in official statistics of mortality (e.g., sex, age, and region), followed by data collection on a scale that allows subsequent identification of case/control pairs with more than the original set of matched factors in common (table 1 and Appendix). The actual size of these subgroups will depend upon the number of originally unmatched factors in each set of associated factors and upon the frequency of these factors in the control group. The effective size of the subgroups (or the quantity of data available for identification of independent effects of originally unmatched factors) will depend upon which set of associated factors is being considered and upon which of the originally unmatched factors in the set is currently operating as a test factor.

For each test factor and each test factor level, one can obtain a series of correlated deviations from expected numbers by *a*) restricting the analysis to such subgroups, *b*) allowing the originally matched factors in each set of associated factors to operate only as controlling factors, and *c*) allowing the originally unmatched factors to operate either as controlling or test factors (*4*). One can then determine the precise significance of these interim findings by following the Mantel–Haenszel procedures and obtaining *a*) for each test factor, a single measure of chi-square whose statistical significance can be computed in the usual way (table 2), *b*) for each test factor level, a series of observed and expected numbers with a single measure of the progression line (table 3), and *c*) for any pair of test factor levels, a single measure of relative risk (tables 4, 5).

OXFORD SURVEY OF CHILDHOOD CANCERS

For nearly a quarter of a century the Oxford Survey has collected registrations of all childhood cancers in England, Scotland, and Wales (notification data) and obtained further information from parents of traced cases and matched controls (interview data) (*3*). Each traced case was paired with a control of the same sex, date of birth, and region. For some unmatched factors (including fetal irradiation), additional information was obtained from family doctors, antenatal clinics, and hospitals (postal data) (*5, 6*).

Since the cases were identified from lists of dead children and controls from lists of live births, there was probably better representation of migrant families (which are biased in favor of young parents) among the traced cases than their matched controls (table 1). This fact is immaterial from the point of view of whether to allow maternal age to operate as a controlling factor in any set of case/control comparisons. If, however, maternal age is also used as a test factor, the expected number of young mothers will certainly be too low if there is better representation of migrant families among cases than controls (tables 3–5).

RESULTS

There were originally two reasons for applying Mantel–Haenszel procedures to Oxford data: 1) to discover whether an obvious excess of fetal irradiation histories in the case group was a genuine finding (table 1) or an artifact due to associations between obstetric radiography and other birth factors of etiologic importance, e.g., sex, date of birth, social class, maternal age, and sibship position; and 2) to discover whether four birth factors (social class, maternal age, sibship position, and fetal irradiation) suspected of influencing the prevalence of childhood leukemias and lymphomas [reticuloendothelial system (RES) neoplasms] had similar effects on other childhood cancers (tables 1–5).

[1] Received March 19, 1975; revised October 1, 1975; accepted October 14, 1975.

[2] Supported by Public Health Service contract 223-75-6001 from the Bureau of Radiological Health, Department of Health, Education, and Welfare.

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[4] The Oxford Survey data were collected by a nationwide network of doctors affiliated with county and county borough health departments.

TABLE 1.—*Original records of matched and unmatched factors (Oxford data)*

Factors and factor levels	RES neoplasms	Other cancers	Controls
Sex: [a]			
Males	3,325	2,646	5,971
Females	2,373	2,175	4,548
Birth years: [a]			
1943–49	1,178	688	1,866
1950–54	1,762	1,401	3,163
1955–59	1,522	1,333	2,855
1960–64	1,003	1,001	2,004
1965–69	233	398	631
Social class: [b]			
I	258	216	371
II	882	669	1,483
III	3,413	2,873	6,479
IV	726	678	1,327
V	419	385	859
Maternal age (in yr): [b]			
15–19	204	205	241
20–24	1,457	1,219	2,362
25–29	1,846	1,591	3,473
30–34	1,260	1,061	2,628
35–39	686	569	1,392
40+	245	176	423
Sibship position: [b]			
1st	2,212	1,740	3,447
2d	1,715	1,524	3,337
3d	872	783	1,851
4th	425	375	899
5th	204	178	453
Later	270	221	532
Fetal irradiation: [b]			
Nil	4,854	4,080	9,403
Probable [c]	276	187	327
Proved [c]	568	554	789
Totals	5,698	4,821	10,519

[a] Matched factors.
[b] Unmatched factors.
[c] Probable exposures: mothers' claims unsupported by written records of the examinations. Proved exposures: hospital records of the X-ray examinations.

TABLE 2.—*Independent effects of several (unmatched) birth factors*

Controlling factors	Factor levels	Effective data for test factors: RES neoplasms	Effective data for test factors: Other cancers	Chi-square values: RES neoplasms	Chi-square values: Other cancers
Sex	2	Nil	Nil	—	—
Birth years	26	Nil	Nil	—	—
Social class	5	1,478.4	1,320.6	14.15 [a]	12.35 [b]
Maternal age	6	1,877.5	1,650.4	17.69 [a]	29.43 [a]
Sibship position	6	1,830.9	1,586.9	16.87 [a]	3.26
Fetal irradiation	3	473.7	404.3	19.07 [c]	24.35 [c]

[a] Significant at the <1% level.
[b] Significant at the <5% level.
[c] Significant at the <0.1% level.

According to the chi-square values in table 2 and *t* values in table 3, all the originally unmatched factors included in the Mantel–Haenszel analysis (i.e., social class, maternal age, sibship position, and fetal irradiation) had exerted independent effects on RES neoplasms, and all except sibship position had exerted independent effects on other cancers. Since less than 11% of the Oxford controls had histories of fetal irradiation (table 1), the quantity of *effective data* was much smaller

TABLE 3.—*Observed and expected numbers for each test factor level*

Test factors and factor levels	RES neoplasms: Observed	RES neoplasms: Expected	RES neoplasms: *t* values	Other cancers: Observed	Other cancers: Expected	Other cancers: *t* values
Social class:						
I	166	139	+3.23 [a]	146	129	+2.12 [b]
II	525	503	+1.51	399	404	−0.34
III	1,535	1,563	−1.35	1,253	1,290	−1.91
IV	379	391	−0.88	399	365	+2.57 [b]
V	228	237	−0.87	203	212	−0.90
	Progressive component		*3.03* [a]	Progressive component		*0.42*
Maternal age (in yr):						
15−	136	120	+2.03 [b]	142	110	+4.13 [c]
20−	1,009	970	+2.05 [b]	842	806	+2.01 [b]
25−	1,169	1,175	−0.27	978	992	−0.72
30−	688	745	−3.18 [a]	588	634	−2.70 [b]
35−	341	344	−0.20	274	287	−1.12
40+	129	118	+1.48	75	70	+0.83
	Progressive component		*2.20* [b]	Progressive component		*3.76* [a]
Sibship position:						
1st	1,187	1,111	+3.82 [a]	919	887	+1.75
2d	1,061	1,096	−1.70	939	958	−0.96
3d	541	578	−2.22 [b]	500	507	−0.43
4th	274	274	+0.04	223	228	−0.46
5th	111	119	−0.96	107	110	−0.40
Later	127	123	+0.46	100	98	+0.20
	Progressive component		*2.35* [b]	Progressive component		*1.11*
Fetal irradiation:						
Nil	555	605	−4.33 [c]	451	502	−4.68 [c]
Probable [d]	114	95	+2.84 [a]	62	58	+0.75
Proved [d]	231	200	+3.14 [a]	242	195	+4.84 [c]
	Progressive component		*3.98* [a]	Progressive component		*4.92* [a]

[a] Significant at the <1% level.
[b] Significant at the <5% level.
[c] Significant at the <0.1% level.
[d] Probable exposures: mothers' claims unsupported by written records of the examinations. Proved exposures: hospital records of the X-ray examinations.

for this factor than for other test factors (tables 2, 3). Nevertheless, an exceptionally high level of statistical significance can be attached to the finding that fetal irradiation had exerted independent effects on RES neoplasms and other cancers (table 2).

In relation to RES neoplasms, the risk for proved radiation exposures relative to nil exposures (table 4) was lower than that for possible exposures (1.50 and 1.41). However, in relation to the other diagnostic group, the risk for proved radiation exposures relative to nil exposures (table 5) was higher than that for possible exposures (1.20 and 1.66). Therefore, in this important respect, the interview data and the postal data have proved to be equally reliable.

The effects of socioeconomic status on the probability of childhood cancer development were largely the result of children from social class I being more likely to develop RES neoplasms than children from lower social classes, since the progression line from the top to the bottom of the social scale only achieved statistical significance in relation to children with RES neoplasms (table 3).

The proportion of mothers under 25 years of age was smaller for the Oxford controls than for the populations from which these children were drawn (*6*). Therefore, no importance should be attached to the fact that in the controlled analysis the observed number of these mothers

TABLE 4.—*RES neoplasms: Relative risks between pairs of test factor levels* [a]

Social class					Maternal age								Sibship position						Fetal irradiation			
I	II	III	IV	V	15–	20–	25–	30–	35–	40+			1st	2d	3d	4th	5th	6th	Nil	Probable	Proved	
I	*1.00*	0.95	0.66	0.58	0.55	*1.00*	0.83	0.72	0.86	0.57	0.51	15–	1st	*1.00*	0.85	0.74	0.95	0.68	0.89	*1.00*	1.50	1.41	Nil
II	1.05	*1.00*	0.92	0.81	0.87	1.20	*1.00*	0.92	0.76	1.02	0.81	20–	2d	1.18	*1.00*	0.92	1.02	1.20	1.17	0.67	*1.00*	0.69	Probable
III	1.52	1.09	*1.00*	1.01	0.91	1.39	1.09	*1.00*	0.91	0.82	1.55	25–	3d	1.35	1.09	*1.00*	0.99	0.89	1.00	0.71	1.45	*1.00*	Proved
IV	1.72	1.23	0.99	*1.00*	1.22	1.16	1.32	1.10	*1.00*	1.21	1.31	30–	4th	1.05	0.98	1.01	*1.00*	0.83	0.97				
V	1.82	1.15	1.10	0.82	*1.00*	1.75	0.98	1.22	0.81	*1.00*	1.02	35–	5th	1.47	0.83	1.12	1.20	*1.00*	1.55				
					1.96	1.23	0.65	0.76	0.98	*1.00*	40+	6th	1.12	0.85	1.00	1.03	0.65	*1.00*				

[a] *See* footnote [c], table 1. Standard risks (1.00) are *in italics*.

TABLE 5—*Other cancers: Relative risks between pairs of test factor levels* [a]

Social class					Maternal age in years								Sibship position						Fetal irradiation			
I	II	III	IV	V	15–	20–	25–	30–	35–	40+			1st	2d	3d	4th	5th	6th	Nil	Probable	Proved	
I	*1.00*	0.88	0.79	0.92	0.31	*1.00*	0.64	0.58	0.49	0.47	1.33	15–	1st	*1.00*	0.90	0.89	1.00	0.98	0.85	*1.00*	1.20	1.66	Nil
II	1.14	*1.00*	0.93	1.16	1.85	1.56	*1.00*	0.90	0.80	0.81	0.61	20–	2d	1.11	*1.00*	0.97	1.09	0.87	1.00	0.83	*1.00*	1.41	Probable
III	1.27	1.08	*1.00*	1.21	0.91	1.72	1.11	*1.00*	0.88	1.00	1.13	25–	3d	1.12	1.03	*1.00*	0.86	0.93	0.95	0.60	0.71	*1.00*	Proved
IV	1.09	0.86	0.83	*1.00*	1.22	2.04	1.25	1.14	*1.00*	0.99	1.34	30–	4th	1.00	0.92	1.16	*1.00*	1.44	1.31				
V	3.22	0.54	1.10	0.82	*1.00*	2.13	1.23	1.00	1.01	*1.00*	1.43	35–	5th	1.02	1.15	1.08	0.69	*1.00*	2.22				
					0.75	1.64	0.88	0.76	0.70	*1.00*	40+	6th	1.18	1.00	1.05	0.76	0.45	*1.00*				

[a] *See* footnote [a] of table 4.

was larger than the expected number (table 3). However, the fact that the observed number of mothers over 40 years (204) was larger than the expected number (188) does suggest that the risk of death from malignant diseases during childhood is positively correlated with maternal age.

There was no indication that sibship position had an effect on cancers other than RES neoplasms, and though first-born children were more at risk of developing RES neoplasms than other children, the risks were roughly the same for second-born children and those born later. In the controlled analysis, the ratios of observed to expected numbers for RES neoplasms were 1.07 for first-born children, 0.97 for second-born children, and 0.96 for those born later (table 3). Alternatively, compared with first-born children, the risk for each higher birth rank was below par, but compared with fifth-born children, only the risk of second-born children was below par (table 4).

DISCUSSION

By comparing a nationwide series of childhood cancers in the Oxford Survey with an equally large series of healthy controls, Stewart et al. (*7*) soon discovered an excess of fetal irradiation histories in the case group. Within 2 years of publishing an interim report based on 547 case/control pairs (by which time the mothers of 1,299 case/control pairs had been interviewed), Stewart et al. (*8*) decided that there must be a nonspecific cancer hazard associated with obstetric radiography. This conclusion was based on retrospective data and was not subsequently ratified by prospective surveys or animal experiments. Therefore, for several years it was widely assumed that the "extra" X-rayed cases (which continued to appear in successive samples of Oxford data) were artifacts produced either by more accurate reporting of X-ray histories by case than control mothers or by hidden associations between obstetric radiography and various "causes" of childhood cancers.

The discovery of equally good standards of reporting by case and control mothers in the Oxford Survey eventually made the first explanation unlikely (*9*), and the discovery of an exception to the rule that prospective surveys were unable to confirm the association eventually made the second explanation unlikely (*10*). Nevertheless, the idea that even during fetal life there is no cancer hazard associated with low-level radiation has remained in circulation. This continued scepticism was largely due to the fact that less than 1 in 1,000 A-bomb survivors who were exposed in utero subsequently developed childhood cancers (*11*); but it was also influenced by the fact that maternal age and sibship position are associated both with obstetric radiography and childhood cancers.

The present investigation has shown that three factors associated with fetal irradiation also exert independent effects on the risk of childhood cancer development. Nevertheless, these joint associations are not responsible for the fact that exposure in utero to diagnostic doses of ionizing irradiation is associated with an exceptionally high risk of developing a neoplastic disease within 15 years of birth. The Mantel–Haenszel analysis has also shown that on no occasion have more straightforward analyses of Oxford data exaggerated the importance of obstetric radiography as a preventable cause of childhood leukemias and solid tumors.

APPENDIX: TECHNICAL DETAILS OF THE MANTEL–HAENSZEL PROCEDURE

A Mantel–Haenszel analysis (*4*) is a reliable procedure for testing, in data from a retrospective survey, whether particular events or circumstances (test factors) have effects that are independent of other events or circumstances (controlling factors) whose effects might cause confusion in a crude analysis because of unsuspected associations between the various factors. The factors under immediate consideration and their marginal distributions are listed in table 1.

There was deliberate matching of Oxford cases and controls for certain characteristics (*5*) (and, therefore, a set of "matched factors" which could not be used as test factors in any controlled analysis). However, the results of analyzing four "unmatched factors" are shown in tables 2–5. The controlling factors in each of these analyses included two matched factors (sex and date of birth) and three unmatched factors (or all the unmatched factors except the one currently serving as a test factor).

The method of analysis was as follows: 1) Let the population be divided into substrata (indexed by i) by all possible combinations of several levels of all the controlling factors. 2) Let the number of cases with test factor level k in substratum i be A_{ki}, and the corresponding number of controls be B_{ki}. 3) Let the total number of cases in substratum i be N_i and the corresponding number of controls be M_i. 4) Let Σ denote summation over substrata i, such that N_iM_i is greater than zero and $(A_{ki}+B_{ki})$ is less than (N_i+M_i) for all k. (Substrata i not satisfying these restrictions make identically zero contributions to the Mantel–Haenszel statistics and hence may be called noninformative.)

The presentations were as follows: In table 2 there appear for each test factor *a*) a quantity known as "effective data" or $[\Sigma N_iM_i/(N_i+M_i)]$, and *b*) a chi-square value for the difference between the observed and expected numbers in each controlled analysis.

The several quantities of effective data should be compared with the constant totals for cases and controls in table 1, since they show not only how much information was lost by having to stratify for each set of controlling factors but also the effect of having as a test factor an event (fetal irradiation) that affected a smaller proportion of controls (10.6%) than cases (15.1%). Also, the chi-square values should be compared with the corresponding number of factor levels because their statistical significance depends upon these (e.g., for social class there were 4 degrees of freedom and for fetal irradiation, 2 degrees).

In table 3, for each test factor level there appear *a*) the observed number of informative cases, ΣA_{ki}, *b*) the expected number of informative cases under the null hypothesis of no difference between the risk at test factor level k and the average risk, or $[\Sigma(A_{ki}+B_{ki})N_i/(N_i+M_i)]$, and *c*) a t value (not corrected for continuity) for the difference between these two numbers.

The progressive components in table 3 were derived from another product of the Mantel–Haenszel analysis, namely the variance–covariance matrix of differences between observed and expected numbers. From this matrix may be obtained t values for many contrasts, of which the most important (after the ones that correspond to individual factor levels) is probably the one provided by a linear scoring system that measures any tendency of the risk to increase or decrease progressively with test factor levels.

Note that in table 3 only contributions from informative strata are considered. Therefore, the total for each set of observed numbers was smaller than the (constant) totals in table 1.

In tables 4 and 5 appear, in square formation , estimates of relative risks given by the formula:

$$R_{kl}=[\Sigma A_{ki}B_{li}/(N_i+M_i)]/[\Sigma A_{li}B_{ki}/(N_i+M_i)]$$

where R_{kl} = the ratio of risk at level k in relation to that at level l. In these tables, level k (numerator) is always the column level and level l (denominator) is always the row level. The square array is necessary because the estimating equation, which has many desirable properties as shown by Mantel and Haenszel (*4*), is not transitively consistent. Therefore, R_{jl} does not necessarily equal $R_{jk}R_{kl}$. It follows that the more reliable estimates are the ones in which the standard (1.00) is set by a relatively large number of cases. For example, social class III accounted for 60% of the cases, and non-X-rayed fetuses for 85% of the cases; also, mothers between 25 and 30 years and first births were relatively common. Therefore, the most reliable estimates for social class differences are the ones in the third column or row, and the most reliable estimates for other differences are the ones in the first column or row.

REFERENCES

(*1*) MANNING MD, CARROLL BE: Some epidemiological aspects of leukemia in children. J Natl Cancer Inst 19:1087–1094, 1957

(*2*) MACMAHON B, NEWILL VA: Birth characteristics of children dying of malignant neoplasms. J Natl Cancer Inst 28:231–244, 1962

(*3*) BITHELL JF, STEWART AM: Pre-natal irradiation and childhood malignancy. Br J Cancer 31:271–287, 1975

(*4*) MANTEL N, HAENSZEL W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748, 1959

(*5*) STEWART AM, BARBER CR: Survey of childhood malignancies—progress report and new ideas. Med Offr 107:3–8, 1962

(*6*) HINDS SW, KINNIER WILSON LM, DRAPER GJ: Childhood malignant disease in Britain 1953–1971. Hlth Soc Serv J 34:880–881, 1974

(*7*) STEWART AM, WEBB J, HEWITT D, et al: Preliminary communication: Malignant disease in childhood and diagnostic irradiation in utero. Lancet 2:447–448, 1956

(*8*) STEWART AM, WEBB JW, HEWITT D: A survey of childhood malignancies. Br Med J 1:1495–1508, 1958

(*9*) HEWITT D, SANDERS BM, STEWART AM: Oxford survey of childhood cancers. Bull Ministr Hlth Lab Serv 25:80–85, 1966

(*10*) MACMAHON B: Prenatal X-ray exposure and childhood cancer. J Natl Cancer Inst 28:1173–1191, 1962

(*11*) JABLON S, KATO H: Childhood cancer in relation to prenatal exposure to atomic-bomb radiation. Lancet 2:1000–1005, 1970