PRENATAL IRRADIATION AND CHILDHOOD CANCER

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SUMMARY

Estimates of the relative risk of childhood cancer, following irradiation during fetal life, are reported. They are based upon an extended case-control investigation of childhood cancer deaths in England Wales and Scotland between 1953 and 1978 comprising 14491 geographically-matched and birth-date-matched case/control pairs.

The estimates were calculated by the Miettinen-Breslow technique. This method of risk estimation limits distortions caused either by confounding factors, or by biassed recall and reporting. The new estimate of relative risk for prenatal x-rays (RR) is about 2.2, compared with earlier crude estimates of about 1.4. The excess risk is equally distributed between the leukaemias and the solid tumours, but is concentrated among cancers with onsets between the ages of 4 and 7 years. The relative risk declined over the 26-year period. This period also saw a reduced number of films per examination, a reduced mean dose of radiation per film, and a reduction in very early fetal exposures. Although the radiation risk has been known for a quarter of a century, there was no evidence of any systematic reduction in the frequency of pregnancy x-rays between 1950 and 1975. During this period of time, about 12 percent of all childhood cancers, and 14 percent of those with onset between the ages of 4 and 7 years, were caused by x-ray examinations. The dose-response relationship was one death per 600 obstetric x-ray examinations; or 3000 deaths per 10^4 man-Gy.

Introduction

The statistical association between fetal radiation exposure and subsequent childhood cancer has been known for a quarter of a century (1,2), and has been confirmed in several independent surveys (3,4). The causal nature of the association is not in doubt but the quantitative relationship between low level radiation and subsequent cancer has remained uncertain. There is a wide difference between risk estimates for low level radiation based on British data (5) and the much lower estimates based on cancer experiences of A-bomb survivors (6). The difference may stem from the different circumstances of exposure and the different age groups concerned but the adequacy of the technical approaches appropriate to the two classes of investigation have each been questioned. In the case of the British study it was possible that the medical associations of diagnostic x-rays, which include illnesses during pregnancy, drugs administered during pregnancy, and a number of possibly relevant socio-demographic factors, may have contributed an artefactual element towards the radiation-Relative Risk estimates. Temporal changes in radiation frequencies and radiation practice, interacting with changing socio-demographic and medical-care factors raise additional questions.

This paper approaches these issues; its objective is to clarify the quantitative relationships between fetal exposure and outcome.

Materials and Methods

This investigation is based upon an extension of the 'Oxford Survey of Childhood Cancer' (OSCC). This is an ongoing case/control study of early cancer deaths. It was begun in 1955 and includes all child deaths (0-15 years) from 1953 to 1978 in England, Scotland and Wales. Each fatal case was paired with a live control matched for sex and date of birth and born in the civil district where the cancer death occurred. Cancer cases were identified through central registers of deaths (London and Edinburgh): and matched controls through local registers of births (boroughs, urban areas and rural districts). Additional controls were identified to replace any 'first choices'who could not be interviewed and the selection-rank of the control eventually adopted, was noted.

1979

Paired interviews of the two mothers were carried out by a doctor or a district nurse from the local Health Department. Intervals between the cancer death and the paired interviews were rarely less than twelve months and general practitioners were usually consulted before approaching the case mother. A number of paired interviews were 'lost', mainly because of the family moving to an unknown address after the cancer death; the family doctor advising against interviews; the mother herself refusing; or difficulty in finding interviewers or controls. In the end, 14,491 paired interviews were obtained, 70% of the 20,740 cancer deaths.

14759

12351

For several important variables, information was sought from more than one source. The data sources for the main items used in the present analysis, and the years during which the information was collected, are given in Table 1. Information on prenatal abdominal x-rays of the mother was obtained

from three sources including the mother herself, the antenatal clinic or general practitioner who requested the x-ray, and the x-ray department itself. As a result it was usually possible to retrieve the reason for the examination, the exact date, the number or estimated number of films, and any abnormal findings. Details of pregnancy illnesses and of drugs administered during pregnancy were also obtained from more than one source.

Statistical methods of analysis

Preliminary explorations of the recorded material were based upon unstandardised estimates of Relative Risk (RR); the estimator was the ratio between those case-control pairs in which the case was exposed to x-rays but the control was not, and those pairs in which the opposite occurred. These simple estimates were used to explore variations according to year of birth and according to the ages at death and at the onset of the tumour; and subsequently to select the variables to be used within a fully standardised quantitative analysis.

These final measurements were based on methods incorporating techniques devised by Miettinen and Breslow for studying large sets of cases with matched controls. This method is directed towards the avoidance of spurious associations between a risk factor and disease occurrence, due to an association between each of them and a third factor. Associations between pairs of variables other than the presence/absence of cancer were studied using the analogous methods of Mantel and Haenszel. Both approaches (MB and MH) are based upon sorting the population into layers which are internally homogeneous with respect to combinations of potential confounding factors.

The MB technique has particular advantages for approaching the problems outlined above. First, it eliminates systematic biases of recall and recording between cases and controls, through incorporating the total numbers of recorded illnesses, drugs and other events within the range of confounding variables. Individual events and individual procedures are then tested for superimposed marginal effects upon cancer-risk, over and above the effects of these totals. Because the OSCC did not begin recording pregnancy drugs until 1964, the MB analyses reported in this paper were performed on a subset of the data-base, containing deaths from 1964 to 1978 and comprising 8059 case/control pairs.

The MB technique also compensates for any biases in the initial selection of the controls, compared with the cases. For example, the most obvious selection bias among the controls was the absence of migrants, because controls were always born and resident in the same District as that in which the child with cancer had died. From this might have stemmed a biassed distribution of migration-related factors with known x-ray associations such as maternal age, sibship position and social class. However, provided that these bias-mediating factors are included among the standardising variables, the effect of the bias is effectively annulled. For the whole period 1953 to 1978, 16.4 percent moved to a new district between birth and death. For the period 1964 to 1978 the proportion was 21.4 percent.

A list of socio-demographic variables appropriate for use in these analyses was selected on the basis of a general exploration of the matrix of associations between all the available variables. This list, as used

consistently within the MB analyses, is provided in Table 2.

RESULTS

a) Validity

The correspondences between the mothers' and the medical reports of pregnancy x-rays and illnesses, and of drugs taken during pregnancy, are shown in Table 3. Mothers' reports of x-rays were confirmed in 63.9 percent of cases and 63.7 percent of controls. In only 5 cases and 7 controls did the antenatal clinic report an x-ray which the mother had not reported. There was no evidence of case/control bias in these respects. Failures to confirm mothers' claims were in some cases due to a failure of the clinic to respond (18 percent of failures) and some mothers misunderstood the difference between a chest x-ray and an abdominal/pelvic x-ray; but in the majority (68 percent) the failure was due to missing case notes or missing x-ray records. We carried out separate studies using both the mothers' claims, and the confirmed reports alone, and the results were similar. All subsequent tabulations in this paper are based upon total claims of x-rays from both sources.

Mothers were asked to report any drugs taken during pregnancy, whether prescribed or self-administered, and general practitioners and antenatal clinics were asked to confirm or deny knowledge of the drug. The results are given in Table 3. Many of the differences between maternal and medical reports could relate to drugs taken other than on prescription. Although the substantial number of drug claims recorded by the clinic and not by the mother suggests that maternal recall was poor, there was no case/control bias in their ability to recall them. Mothers of cases failed to recall 76.5 percent of drugs recorded by the clinic, compared with 78.5 percent not recalled by control mothers. Studies based on all

drug claims, or on claims with clinical records only, produced similar estimates of radiation-RR. The subsequent analyses reported in this paper are based upon all claims.

The relationships between claimed and confirmed illnesses during pregnancy were examined in a similar manner to those for drugs. Maternal recall of illnesses recorded by the general practitioner was better than for drugs. Case mothers failed to recall 49.6 percent and control mothers 53.3 percent of illnesses recorded by the general practitioner; and the general practitioner had no knowledge of 63.0 percent of illnesses recalled by case mothers, and 60.6 percent of illnesses recalled by control mothers. This small asymmetry may indicate a slight excess of self-treated disorders among the case mothers. Subsequent analyses in this paper are based upon all claims of illness. Conflicts of interpretation between the mother and the clinic were decided in favour of the clinic.

The frequencies of x-rays and of potential confounding factors were similar among controls of different selection-ranks, and analyses limited to early or late ranks did not affect our estimate of radiation-RR.

b) Year of birth, year of death and x-ray exposure

The calendar years of birth and death of the 14,491 case-control pairs are shown in Table 4. Cohorts complete from birth to 15 years of age (i.e. 1953 to 1962 births) are shown between the horizontal lines. During this decade, eighty percent of cases were matched with controls. Table 5 shows the proportions of cases and controls x-rayed, together with the average number of films per examination, in 20 successive two-year cohorts.

For both groups of children there was a period before 1950 when the risk of receiving a prenatal x-ray was relatively small, followed by two periods of high exposure (1952-57 and 1970-78). The proportion receiving x-rays was greater for cases (about 15 percent) than for controls (about 11 percent). The average number of films per examination was also somewhat greater among cases (1.9) than among controls (1.7). The numbers of films per examination were greater for the period 1946-1957, than for earlier or later examinations.

The exposure data recorded in this survey can be compared with the results of a national survey carried out in 1957 (7). It showed an exposure rate of 11.4 percent compared with our own result (among controls) of 13.5 percent in 1956-57. A second national survey in 1977 (8) gave an exposure rate of 4.2 percent; our own 1976-77 estimate of 9 percent is based on numbers too small to permit valid comparison.

Table 6 shows 17 cohorts divided into 8 age-at-death groups. Each of the 136 cells of the table displays the ratio between those radiation-discordant pairs in which only the case, or only the control, was x-rayed. The row and column totals give both crude case-control ratios and 'fitted' ratios. The latter were obtained through fitting curves with linear and quadratic terms (through the maximum likelihood method) to the values in the body of the table.

The fitted ratios show a high RR for cancer deaths occurring between 4 and 7 years of age and a low RR for births occurring between 1958 and 1967. The major part of the temporal variation is characterised as a steady decline.

The increase in the period 1968-78 is based on small numbers, but the quadratic term of the fitted ratios was statistically significant. Results were similar when we used age-at-onset instead of age-at-death.

c) Drugs, Illnesses and X-rays

We conducted a preliminary series of case-control comparisons relating to pregnancy illnesses, and then to pregnancy drugs, standardised according to the socio-demographic factors listed in Table 2. We also studied the relationships between the various social and medical factors using the MH method. The objective was to select groups of illnesses and drugs to be included jointly in a substantive MB analysis involving all those factors which might have operated as confounding factors or as independent risk factors. The final selection included all of those with statistically significant associations in the preliminary analyses, and several others with associations which did not reach statistical significance.

Tables 7 to 9 show the results of an MB analysis of 41 factors, grouped into three sets. The log-linear coefficients (β) are equivalent to the natural logarithm of the relative risk between adjacent levels of each factor. Standard errors and significance tests (t-tests) are shown. Where significant coefficients exist for two-level factors (e.g. presence/absence) they are presented in the conventional manner. Other RR's can be calculated as exp(β).

The greatest RR, although not quite significant, was for a small group of children (21) whose epileptic mothers were on maintenance doses of phenytoin or other anti-convulsant drugs (relative risk 3.05). The greatest

significant RR related to obstetric x-ray examinations (RR = 2.25). This result was similar for the leukaemias and for the solid cancers. There were in addition 5 pregnancy illnesses and a single pregnancy drug which exhibited independent significant risk-associations.

The radiation-RR of 2.25 is appreciably higher than earlier OSCC estimates of around 1.4 (2,5,9). Earlier estimates made allowance for socio-demographic factors, but this is the first time that simultaneous allowance has been made for pregnancy illnesses and drugs. Until now it was possible to insist that the reported effects of prenatal x-rays might be the result of associated illnesses or associated medical treatments (10). Such associations exist, and will be studied in detail in subsequent reports, but from the point of view of our present analysis it is clear that they masked rather than exaggerated the cancer effects of prenatal x-rays

DISCUSSION

Our objective was to estimate the RR of childhood cancer following fetal irradiation, taking full account of potential confounding factors. The relevant socio-demographic factors, once identified, were used consistently in all subsequent analyses in order to minimise the effects of bias in the selection of controls, biassed recall of pregnancy events, biassed contemporary recording, and biassed retrieval of recorded data at the time of subsequent enquiries. The new estimates were also standardised for the presence or absence of a range of pregnancy illnesses and pregnancy drugs, and were related to the type of cancer, the age-at-death of the child, the age-at-onset of the cancer, and the year in which the child was born. The power of the methods used, combined with the size of the extended data set and the detail of the several cross-checked sources of information, offer a direct population-based estimate of radiation-RR in the fetus whose accuracy is unlikely to be bettered.

The radiation-RR was larger than previously suspected. The confounding factors had masked rather than exaggerated its true extent. Over the whole period it was about 2.25, reducing from greater values in the earlier years to a lower value in the later years. It was greater for cancers with onsets between the ages of 4 and 7 years. Using the results of the MB analysis we calculate an additional factor of 1.09 for these onsets, raising the radiation-RR to about 2.45 for cancers diagnosed between 4 and 7 years. There was no difference in these respects between the leukaemias and the solid tumours.

Our confidence in the accuracy of the estimate is reinforced by the following considerations.

a) we obtained the same results whether we used the mothers' testimony on the question of x-rays, or the testimony of the medical records made at the time. The alternative use of the mothers' and the medical records of illnesses or drugs, likewise made no substantive difference to the estimates of radiation-RR.

b) In a previously reported investigation (11) it was shown, that the mothers' claims of pre-pregnancy and post-pregnancy x-rays, in the mother or in the father, were not associated with the risk of subsequent cancer in the child. This would almost certainly have appeared as an artefact if serious subsequent bias of recall of x-ray exposure had occurred.

c) The RR declined over the major part of the investigation, consistently with measured reductions in numbers of films per examination, and known reductions in the dose delivered per film. This is counter to the pattern which might have been expected if an increasing general knowledge of the cancer producing effects of radiation had resulted in an x-ray-specific positive bias of recall or of recording among the cancer cases.

The proportion of all cases of childhood cancer attributable to medical x-rays can be calculated as $x(RR-1)/[x(RR-1)+1]$, where x is the proportion of the population exposed. Using the 11 percent of controls as an indicator of population exposure ($x = 0.11$), about 12 percent of all cancers are attributable to medical radiation. In the age group 4 to 7 years the radiation-attributable proportion was rather larger, about 14 percent. For any child with cancer in this age group who had in fact been irradiated, we can calculate that there was a 59 percent probability ((RR-

1)/RR) that his x-ray caused his cancer.

Doses of x-rays received by the children in this study were not individually measured. Routine estimation and recording of obstetric x-ray exposures is not generally undertaken. Stewart and Kneale (5) estimated that the mean fetal dose per film from this source declined from about 4.60 mGy (= 460 mRad) in 1943-49 to about 2.00 mGy (=200mRad) in 1960-65. This corresponds reasonably well with the 1957 estimate of the Adrian Committee (7) of 4.47 mGy (mean fetal gonadal dose). The National Radiological Protection Board (12) estimated the mean fetal gonadal dose in 1977 as 3.40 mGy, rather larger than the estimate of Stewart and Kneale. UNSCEAR (13) estimated the mean fetal dose per film at 18.0 mGy in 1947-50 and 5.0 mGy in 1958-60, but this was not specific to the United Kingdom. A reasonable overall estimate of mean fetal dose in our own study, corresponding with about 1959, would be 3.00 mGy per film, or 5.00 mGy (= 500 mRad) per obstetric x-ray examination.

Assuming one in 650 births develop cancer before age 15 (14), and using the numbers of films and the doses then prevailing, this gives a dose-response estimate of approximately one death per 600 obstetric radiological examinations 3000 deaths per 10^4 man-Gy (95% confidence limits 900 per 10^4 man-Gy and 6900 per 10^4 man-Gy). This is substantially greater than previous estimates of cancer risk following irradiation in utero. UNSCEAR (13) estimated 200 to 250 deaths per 10^4 man-Gy, and the Beir committee (15) suggested a maximum risk of 600 deaths per 10^4 man-Gy.

Two additional points arise from this investigation. First, some of the drugs and illnesses included among the list of 'confounders', showed independent statistically significant relationships with the risk of cancer. Second, the dose response estimate suggests (on a linear hypothesis) that as many cancer cases might arise from background radiation as from medical radiation, and that it might therefore be possible to demonstrate a geographical co-variation between incidence and measured background. Both of these issues are the subjects of separate investigations.

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Table 1

OSCC Data Sources

Variables	Data Sources
Date of Birth	Interview & Death or Birth Certificates
Date of Death	Interview & Death Certificates
Cancer Age(1)	Interview & Hospital Records
Maternal Age	Interview Only
Social Class(2)	Interview and Death Certificates
Sibship Position	Interview Only
Prenatal X-rays	Interview; Antenatal Clinic or GP and X-ray Department(3)
Pregnancy Illnesses	Interview and Antenatal Clinic or GP
Pregnancy Drugs(4)	Interview and Antenatal Clinic or GP

(1) Age at diagnosis

(2) Based on father's occupation

(3) These records include dates, reasons, films and x-ray findings

(4) For this item there was no data collection before 1964. For all other items the data collection period was 1953-1978.

Table 2

Socio-Demographic Variables Included in the

Miettinen/Breslow Analysis of OSCC Data

Factors

1. Prenatal x-ray (R)
2. Sibship position (S)
3. Maternal age (M)
4. Social class (C)
5. S^2
6. M^2
7. C^2
8. S x R
9. M x R
10. C x R
11. R x Birth year (B)
12. R x Cancer age (A)
13. R x Tumour type (T)
14. R x B^2
15. R x A^2
16. R x A x T

Table 3

Correspondence Between Interview Data and Contemporary Records of Certain Antenatal Events For 8059 Case/Control Pairs from the Years 1964-78.

Events No. of women claiming	Data Sources	No. of Events Claimed Cases	Controls	Ratio
Abdominal X-rays 1179 Cases 986 Controls	Mother & Clinic	753	628	1.20
	Clinic says chest x-ray only	62	47	1.32
	Clinic fails to reply	74	61	1.21
	Clinic says records destroyed	285	243	1.17
	Clinic only claims	5	7	0.71
	Total	1179	986	1.20
Pregnancy Drugs 2388 Cases 1926 Controls	Mother & Clinic	467	353	1.32
	Mother only	1599	1141	1.40
	Clinic only	1523	1286	1.18
	Total	3589	2780	1.29
Pregnancy Illnesses 4359 Cases 3783 Controls	Mother & Clinic	1214	992	1.22
	Mother only	4103	3263	1.26
	Clinic only	1194	1133	1.05
	Total	6511	5388	1.21

Clinics providing information were not told whether they were dealing with case or control mothers.

TABLE 4 Temporal distribution of years of birth and years of death. (matched pairs only)

Year of birth	Year of Death																								
	1953	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
1939	1																									
40			1	4																						
41			9	6	2																					
42			4	12	10																					
43	19		9	15	12	14																				
44	27	16	6	15	21	10	8	1																		
45	30	28	13	9	15	13	9	12	17																	
46	40	36	41	19	15	10	19	25	45	20																
47	60	44	48	32	27	13	17	17	35	36	13															
48	66	55	46	38	38	21	20	10	33	40	45	21														
49	71	61	54	54	23	42	28	14	43	35	25	24	16													
50	59	72	51	53	36	47	33	30	28	29	48	40	31	15												
51	71	62	81	50	45	41	40	43	27	33	17	26	30	38	16											
52	52	58	79	65	39	54	42	43	27	28	26	23	25	26	35	12										
53	30	49	80	59	68	56	50	43	32	30	40	24	32	34	34	28	20									
54		21	51	68	65	58	57	51	34	33	40	30	31	25	35	32	30	10								
55			21	41	43	75	64	63	53	28	40	34	29	38	31	24	29	24	8							
56				25	49	58	73	62	55	46	49	37	33	29	32	26	28	27	11	8						
57					24	42	57	64	58	55	45	40	31	32	32	32	23	26	25	23	12					
58						27	54	70	88	58	73	48	48	39	34	28	22	23	30	22	21	14				
59							23	55	73	78	69	69	62	31	43	32	25	28	17	15	15	22	7			
60								19	49	79	68	60	62	51	48	39	28	32	34	18	23	17	21	6		
61									21	55	57	59	79	70	37	29	29	27	28	19	23	19	29	18	7	
62										24	56	55	58	61	62	43	37	25	27	21	23	27	21	21	28	10
63											33	52	56	78	71	70	38	37	37	26	16	23	16	18	12	21
64												29	48	62	54	67	54	56	39	32	20	14	18	26	16	19
65													19	49	68	57	45	35	31	45	16	17	21	18	13	21
66														29	56	63	58	53	41	39	25	21	30	17	21	15
67															35	38	53	51	44	42	35	39	24	17	25	19
68																[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	22	20	[illegible]
69																	[illegible]	20	38	52	35	43	27	24	18	17
70																		25	33	45	34	36	30	32	25	18
71																			20	37	29	30	39	33	19	30
72																				19	20	33	24	27	33	22
73																					19	26	22	23	19	33
74																						11	19	25	21	22
75																							21	17	19	17
76																								13	18	20
77																									8	20
78																										6
Percentage ascertainment	83	83	83	75	76	76	79	80	78	78	78	77	75	73	73	65	63	63	62	61	53	56	53	57	52	59
	1953	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78

NOTE: complete cohorts are enclosed between bold lines

Table 5

Proportions of X-rayed Cases and Controls by Year of Birth

Birth Year	CC pairs	X-rayed Children		Mean Films per examination	
		Cases %	Controls %	Cases	Controls
1940-41	22	4.5	18.2	-	1.0
1942-43	95	9.5	5.3	2.0	1.0
1944-45	251	8.0	7.6	2.0	1.2
1946-47	616	11.5	3.4	3.1	2.6
1948-49	927	13.1	6.9	2.2	1.9
1950-51	1199	15.2	9.8	2.7	2.3
1952-53	1353	16.5	12.6	2.3	2.3
1954-55	1316	19.7	13.1	2.3	2.2
1956-57	1269	19.3	13.5	2.1	2.0
1958-59	1364	12.6	10.6	1.8	1.7
1960-61	1262	12.0	9.8	1.5	1.4
1962-63	1205	12.3	11.8	1.5	1.3
1964-65	1009	14.6	12.3	1.5	1.3
1966-67	890	12.8	11.9	1.3	1.4
1968-69	627	15.1	11.6	1.5	1.5
1970-71	515	19.6	15.3	1.1	1.3
1972-73	320	21.3	16.9	1.3	1.4
1974-75	172	22.1	16.3	1.1	1.5
1976-77	79	15.2	8.9	1.2	1.3
1978	6	16.7	50.0	1.0	1.7
Total	14491	15.0	11.2	1.9	1.7

TABLE 6

Radiation-Discordant Case/Control Pairs Distributed by Year of Birth and Age at Death

(Showing number of pairs in which only the case (a) or only the control (b) was x-rayed.)

Year of birth	Age at death (years)									
	0,1	2,3	4,5	6,7	8,9	10,11	12,13	14,15	Total	Relative (RR
	a/b	a/b	a/b	a/b	a/b	a/b	a/b	a/b	a/b	Crude Fit
1940-3	-/-	-/-	-/-	-/-	-/2	2/-	4/3	2/-	8/6	1.33 1.7
1944-5	-/-	-/-	-/-	-/3	5/3	2/-	3/2	4/5	14/14	1.00 1.9
1946-7	-/-	-/-	1/-	8/-	12/2	7/1	5/2	11/9	44/15	2.93 2.0
1948-9	-/-	2/-	14/7	16/4	17/11	8/2	16/8	11/6	84/38	2.21 2.0
1950-1	3/-	17/16	22/9	23/12	19/5	11/10	11/12	10/13	116/77	1.51 1.7
1952-3	10/7	30/20	26/15	25/19	16/16	18/7	17/13	23/21	165/118	1.40 1.5
1954-5	17/17	41/22	41/19	28/20	23/19	20/10	17/14	20/7	207/128	1.62 1.6
1956-7	25/19	42/15	21/24	43/15	19/10	18/12	6/15	14/6	188/116	1.62 1.7
1958-9	24/14	35/27	20/21	26/20	18/12	12/10	5/9	11/9	151/122	1.24 1.2
1960-1	26/15	23/27	27/18	10/9	18/12	13/11	11/7	4/9	132/108	1.22 1.2
1962-3	24/16	29/28	29/16	14/21	8/14	8/5	7/10	4/4	123/114	1.08 1.0
1964-5	20/19	33/31	24/15	17/18	9/7	8/4	6/2	-/-	117/96	1.22 1.2
1966-7	27/26	24/15	17/15	12/13	7/13	4/4	-/-	-/-	91/86	1.06 1.0
1968-9	16/9	17/25	20/11	16/4	8/5	-/-	-/-	-/-	77/54	1.43 1.4
1970-1	27/15	21/17	21/11	8/8	-/-	-/-	-/-	-/-	77/51	1.51 1.5
1972-3	21/17	12/9	11/6	-/-	-/-	-/-	-/-	-/-	44/32	1.38 1.4
1974-6	25/13	4/5	-/-	-/-	-/-	-/-	-/-	-/-	29/18	1.61 1.7
Total	265/187	330/257	294/187	246/167	179/131	131/77	108/97	114/90	1667/1193	
Crude RR	1.42	1.28	1.57	1.47	1.37	1.70	1.11	1.27		1.40
Fitted RR	1.73	1.95	2.07	2.06	1.92	1.68	1.45	1.25		

Table 7

Miettinen/Breslow Analysis of 41 Factors
(1) Radiation Exposure and Socio-Demographic Factors of 8059 Case/Control Pairs

Factors	Change[1] in ln (Relative Risk) β	SE	t-test	Relative Risk[1]
1. Prenatal x-ray (R)[2]	0.80946	0.3005	+ 2.69 **	2.25
2. Sibship position (S)	0.01115	0.0166	+ 0.67	
3. Maternal age (M)	- 0.02458	0.0042	- 5.86 ***	
4. Social class (C)	- 0.02296	0.0208	- 1.10	
5. S^2	0.01027	0.0043	+ 2.36 *	
6. M^2	0.00164	0.0005	+ 3.55 ***	
7. C^2	- 0.00808	0.0067	- 1.20	
8. S x R	- 0.00625	0.0400	- 0.16	
9. M x R	0.01889	0.0099	+ 1.91	
10. C x R	- 0.00581	0.0320	- 0.18	
11. R x birth year (B)	- 0.02130	0.0181	- 1.17	
12. R x cancer age (A)	- 0.00033	0.0017	- 0.19	
13. R x type of tumour (T)	- 0.06378	0.1079	- 0.59	
14. R x B^2	0.00319	0.0015	+ 2.06 *	
15. R x A^2	- 0.00003	0.0000	- 1.23	
16. R x A x T	-0.00100	0.0020	- 0.49	

(1) Per unit change in level of factor.
(2) No. of x-rayed cases 1179.

* $0.01 < p < 0.05$
** $0.001 < p < 0.01$
*** $p < 0.001$

Table 8

Miettinen-Breslow Analysis of 41 Factors

(2) Pregnancy Illnesses

Factors	Number of cases	Change[1] in ln (Relative Risk) β	SE	t-test	Relative Risk[1]
17. Acute respiratory infections	411	0.58300	0.1063	+ 5.48 ***	1.79
18. Acute gastric infections	137	0.26808	0.1563	+ 1.71	
19. Other acute infections	208	0.30031	0.1281	+ 2.34 *	1.35
20. Toxaemia	1105	-0.02217	0.0693	- 0.32	
21. Anaemia	1280	0.06863	0.0665	+ 1.03	
22. Caesarean section	113	0.10697	0.1667	+ 0.64	
23. Other pregnancy complications	1354	0.01096	0.0627	+ 0.17	
24. Varicose veins & thrombosis	98	-0.33812	0.1091	- 3.10 **	0.71
25. Other cardiovascular	201	0.07591	0.0971	+ 0.78	
26. Arthritis	28	0.11733	0.1492	+ 0.79	
27. Epilepsy and migraine	71	0.23493	0.1059	+ 2.22 *	1.26
28. Mental illness	74	0.22341	0.1078	+ 2.07 *	1.25
29. All illnesses	4359	0.12957	0.0446	+ 2.90 **	1.14

(1) per unit change in level of factor.

* $0.01 < p < 0.05$
** $0.001 < p < 0.01$
*** $p < 0.001$

Table 9

Miettinen-Breslow Analysis of 41 Factors

(3) Pregnancy Drugs

	Factors	Number of cases	Change[1] in ln (Relative Risk) β	SE	t-test	Relative Risk[1]
30.	Antibiotics	386	0.11220	0.1106	+ 1.01	
31.	Sulphonamides	71	0.18623	0.3041	+ 0.61	
32.	Anti-pyretics and Analgesics	270	0.34815	0.1185	+ 2.94 **	1.42
33.	Steroids	32	0.24988	0.3191	+ 0.78	
34.	Gonadal hormones	206	0.21473	0.1256	+ 1.71	
35.	Vaccines	138	0.30627	0.1605	+ 191	
36.	Anti-convulsants	21	1.11422	0.5783	+ 1.93	3.05
37.	Hypnotics and sedatives	836	-0.00475	0.0812	- 0.06	
38.	Bronchial anti-spasmodics	50	0.26920	0.2351	+ 1.15	
39.	Anti-nauseants	533	0.01933	0.0916	+ 0.21	
40.	Anti-hypertensives	52	0.16296	0.2286	+ 0.71	
41.	All drugs	2388	0.04674	0.0577	+ 0.81	1.05

(1) per unit change in level of factor.

* $0.01 < p < 0.05$
** $0.001 < p < 0.01$
*** $p < 0.001$