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Patterns and Temporal Trends in the Incidence of Malignant Disease in Children: II. Solid Tumours of Childhood

V. Blair and J.M. Birch

Incidence patterns and trends, in children, of individual types of non-reticulo-endothelial solid tumours and of all cancers combined (including leukaemia and lymphoma) were analysed. The study included 3360 cases diagnosed in residents under 15 years of age of the North Western Regional Health Authority area of England during 1954–1988. Log-linear modelling identified significant increases of juvenile astrocytoma (average quinquennial increase 15%) in males, of medulloblastoma (19%) and neuroblastoma (17%) in females, and of non-skin epithelial tumours (18%) overall, and a significant decrease of unspecified malignant neoplasms around 1974 by approximately 80%. The χ^2 trend test identified significant increases in gonadal germ cell tumours and skin cancers, and borderline significant increases in craniopharyngioma and hepatoblastoma. The incidence of all cancers combined increased significantly in those aged under 1 year (8%), 1–4 years (5%) and 10–14 years (8%). Age–sex patterns were similar to those in other Caucasian populations. Studies of incidence trends can provide the basis for investigations of the aetiology of childhood cancers.

Key words: childhood, neoplasms, incidence
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INTRODUCTION

NON-RETICULO-ENDOTHELIAL (RE) solid tumours (hereafter referred to as solid tumours) accounted for 55% of childhood malignancies in England and Wales during 1971–1980, just under half of these occurred in the central nervous system (CNS) [1]. There are fewer published studies of incidence of solid tumours in childhood than of haematopoietic and RE neoplasms. Studies of incidence patterns in neoplastic disease are important for several reasons; they may provide an indication that levels of environmental carcinogens are changing, identify aetiological factors which could ultimately lead to the development of preventative measures and supply information for the planning

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Table 1. Number of cases and average annual incidence (per million population) by age group, sex and diagnosis, 1954–1988

Diagnostic group	Sex	Age group (years) <1 No.	<1 Rate	1–4 No.	1–4 Rate	5–9 No.	5–9 Rate	10–14 No.	10–14 Rate	0–14 No.	0–14 Rate	χ^2 tests for heterogeneity *P* values: Age	Sex
Ependymoma	M	8	6.8	28	6.1	13	2.3	8	1.3	57	3.5	0.00004	
	F	8	7.5	27	6.0	8	1.4	11	2.0	54	3.5	0.00003	
	Total	16	7.1	55	6.1	21	1.9	19	1.6	111	3.5	<0.00001	1.0
Adult astrocytoma	M	2	1.6	15	3.2	21	3.7	26	4.6	64	3.6	0.42	
	F	1	0.9	12	2.8	32	5.9	16	2.9	61	3.7	0.009	
	Total	3	1.3	27	3.0	53	4.8	42	3.8	125	3.6	0.04	1.0
Juvenile astrocytoma	M	4	3.4	35	7.5	32	5.6	33	5.6	104	6.0	0.36	
	F	1	1.0	26	5.8	32	6.0	37	6.8	96	5.8	0.13	
	Total	5	2.2	61	6.7	64	5.8	70	6.2	200	5.9	0.09	0.9
Medulloblastoma	M	2	1.7	33	7.0	47	8.3	21	3.5	103	6.0	0.002	
	F	1	0.8	23	5.3	24	4.5	10	1.7	58	3.7	0.007	
	Total	3	1.3	56	6.2	71	6.4	31	2.6	161	4.9	0.00002	0.001
Craniopharyngioma	M	0	0.0	4	0.9	11	1.9	10	1.8	25	1.4	*	
	F	0	0.0	1	0.2	11	2.0	6	1.1	18	1.0	*	
	Total	0	0.0	5	0.6	22	2.0	16	1.4	43	1.2	0.01	0.37
Meningioma	M	2	1.6	2	0.4	1	0.2	3	0.5	8	0.4	*	
	F	0	0.0	6	1.3	1	0.2	6	1.1	13	0.8	*	
	Total	2	0.8	8	0.9	2	0.2	9	0.8	21	0.6	*	0.22
Other intra-cranial and intra-spinal neoplasms	M	6	5.2	21	4.6	47	8.3	21	3.6	95	5.5	0.006	
	F	6	5.6	15	3.4	30	5.5	21	3.9	72	4.4	0.36	
	Total	12	5.4	36	4.0	77	6.9	42	3.7	167	5.0	0.003	0.16
Neuroblastoma	M	27	23.4	70	14.9	18	3.2	0	0.0	115	7.5	<0.00001	
	F	22	20.4	63	14.4	8	1.5	1	0.2	94	6.6	<0.00001	
	Total	49	21.9	133	14.7	26	2.4	1	0.1	209	7.1	<0.00001	0.29
Retinoblastoma	M	22	19.1	34	7.2	2	0.4	0	0.0	58	3.9	<0.00001	
	F	17	15.1	27	6.0	4	0.7	0	0.0	48	3.3	<0.00001	
	Total	39	17.2	61	6.7	6	0.5	0	0.0	106	3.6	<0.00001	0.48
Wilms' tumour	M	20	17.5	63	13.6	13	2.3	4	0.7	100	6.6	<0.00001	
	F	10	10.4	67	15.3	15	2.8	3	0.6	95	6.6	<0.00001	
	Total	30	14.0	130	14.4	28	2.5	7	0.7	195	6.6	<0.00001	1.0

Continued over.

Table 1.Continued

Diagnostic group	Sex	Age group (years) <1 No.	<1 Rate	1–4 No.	1–4 Rate	5–9 No.	5–9 Rate	10–14 No.	10–14 Rate	0–14 No.	0–14 Rate	χ^2 tests for heterogeneity *P* values: Age	Sex
Hepatoblastoma	M	4	3.7	7	1.5	3	0.5	0	0.0	14	0.9	*	
	F	6	5.4	0	0.0	0	0.0	0	0.0	6	0.4	*	
	Total	10	4.5	7	0.8	3	0.3	0	0.0	20	0.7	*	0.09
Osteosarcoma and chondrosarcoma	M	0	0.0	2	0.4	9	1.6	32	5.7	43	2.3	<0.00001	
	F	0	0.0	0	0.0	12	2.2	40	7.3	52	2.8	<0.00001	
	Total	0	0.0	2	0.2	21	1.9	72	6.5	95	2.5	<0.00001	0.25
Ewing's sarcoma	M	0	0.0	2	0.4	12	2.2	14	2.5	28	1.5	*	
	F	0	0.0	4	0.9	11	2.0	20	3.6	35	2.0	*	
	Total	0	0.0	6	0.6	23	2.1	34	3.0	63	1.7	0.0002	0.27
Rhabdomyosarcoma	M	7	6.0	37	7.9	21	3.7	13	2.3	78	4.8	0.0003	
	F	5	4.5	22	5.0	11	2.0	12	2.2	50	3.2	0.03	
	Total	12	5.3	59	6.5	32	2.9	25	2.2	128	4.0	<0.00001	0.03
Other soft tissue sarcoma	M	5	4.5	5	1.1	8	1.4	9	1.6	27	1.6	*	
	F	4	3.5	8	1.8	6	1.1	8	1.5	26	1.6	*	
	Total	9	4.0	13	1.4	14	1.3	17	1.6	53	1.6	0.03	0.96
Non-gonadal germ cell tumours	M	2	1.8	3	0.7	6	1.1	5	0.8	16	0.9	*	
	F	1	0.8	20	4.7	5	0.9	3	0.5	29	2.0	*	
	Total	3	1.3	23	2.6	11	1.0	8	0.7	45	1.4	0.002	0.04
Gonadal germ cell tumours	M	2	2.0	18	3.9	2	0.3	1	0.2	23	1.5	*	
	F	0	0.0	0	0.0	3	0.6	19	3.4	22	1.2	*	
	Total	2	1.0	18	2.0	5	0.4	20	1.8	45	1.3	0.009	1.0
Epithelial neoplasms except skin	M	0	0.0	4	0.8	6	1.1	26	4.4	36	1.9	*	
	F	3	2.7	5	1.2	5	0.9	14	2.5	27	1.6	*	
	Total	3	1.3	9	1.0	11	1.0	40	3.5	63	1.8	0.00002	0.34
Skin neoplasms	M	0	0.0	3	0.6	1	0.2	5	0.9	9	0.5	*	
	F	0	0.0	1	0.3	4	0.7	11	1.9	16	0.9	*	
	Total	0	0.0	4	0.4	5	0.5	16	1.4	25	0.7	*	0.12
Unspecified malignant neoplasms	M	3	2.4	11	2.3	4	0.7	11	1.9	29	1.7	*	
	F	2	1.6	8	1.7	6	1.1	7	1.4	23	1.4	*	
	Total	5	2.0	19	2.0	10	0.9	18	1.7	52	1.5	0.17	0.53
All malignant and all central nervous system†	M	140	121.1	731	157.4	537	94.7	466	81.0	1874	112.3	<0.00001	
	F	113	104.4	577	131.5	398	73.7	398	72.6	1486	93.8	<0.00001	
	Total	253	113.0	1308	144.8	935	84.5	864	76.9	3360	103.3	<0.00001	<0.00001

M, male; F, female. * Not done. † Includes 1407 cases of leukaemia and lymphoma and 26 rare diagnoses.

Table 2. Number of cases and average annual incidence rate (per million population) by time period and diagnosis, 1954–1988

Diagnostic group	Time period														χ^2 test P values	
	1954–1958		1959–1963		1964–1968		1969–1973		1974–1978		1979–1983		1984–1988			
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	Heterogeneity	Trend
Ependymoma	18	3.9	16	3.4	14	2.7	20	3.8	17	4.0	15	3.8	11	3.0	0.9	0.9
Adult astrocytoma	16	3.3	19	3.7	18	3.4	20	3.6	17	3.4	17	3.9	18	4.6	1.0	0.4
Juvenile astrocytoma	30	6.0	21	4.2	28	5.3	38	6.8	23	4.7	27	6.1	33	8.7	0.2	0.1
Medulloblastoma	18	3.7	22	4.5	26	4.9	21	3.9	23	4.8	32	7.6	19	5.0	0.1	0.05
Craniopharyngioma	4	0.8	7	1.3	6	1.1	5	0.9	5	0.9	6	1.5	10	2.4	0.3	0.1
Meningioma	1	0.2	4	0.9	3	0.6	4	0.8	2	0.4	3	0.7	4	0.9	0.8	0.3
Other intra-cranial and intra-spinal neoplasms	20	4.0	16	3.2	22	4.1	28	5.0	24	5.0	29	6.9	28	7.4	0.06	0.002
Neuroblastoma	27	5.9	28	6.0	36	7.1	30	6.2	24	6.5	30	9.0	34	9.9	0.3	0.02
Retinoblastoma	17	3.7	14	3.1	20	4.0	15	3.1	12	3.5	6	1.9	22	6.4	0.1	0.4
Wilms' tumour	27	5.8	28	6.1	29	5.7	32	6.3	27	7.5	25	7.6	27	7.7	0.9	0.2
Hepatoblastoma	1	0.2	2	0.4	3	0.6	5	1.1	2	0.6	3	0.9	4	1.1	0.6	0.1
Osteosarcoma and chondrosarcoma	16	3.1	12	2.1	9	1.7	17	2.9	14	2.5	16	3.2	11	2.5	0.8	0.8
Ewing's sarcoma	8	1.6	14	2.6	8	1.5	11	1.9	6	1.1	10	2.0	6	1.4	0.6	0.5
Rhabdomyosarcoma	17	3.5	24	5.1	25	4.8	19	3.7	15	3.5	17	4.4	11	2.8	0.7	0.4
Other soft tissue sarcoma	8	1.6	7	1.4	10	1.9	8	1.6	3	0.6	7	1.9	10	2.4	0.5	0.6
Non-gonadal germ cell tumours	7	1.5	7	1.5	2	0.4	4	0.7	10	2.4	9	2.2	6	1.7	0.1	0.2
Gonadal germ cell tumours	2	0.4	4	0.8	3	0.6	13	2.5	9	1.8	8	1.9	6	1.7	0.04	0.01
Epithelial neoplasms except skin	5	1.0	5	0.9	11	2.1	8	1.5	10	2.0	13	2.6	11	2.6	0.2	0.01
Skin neoplasms	2	0.4	2	0.4	0	0.0	3	0.5	7	1.2	2	0.5	9	2.1	0.002	0.002
Unspecified malignant neoplasms	10	2.1	17	3.3	8	1.5	11	2.0	3	0.7	1	0.2	2	0.5	0.001	0.0002
All malignant and all central nervous system*	445	92.4	465	95.0	486	92.7	563	105.7	480	107.7	461	115.3	460	121.1	0.00001	<0.00001

* Includes 1407 cases of leukaemia and lymphoma and 26 rare diagnoses.

Table 3. Estimates of relative risks in females compared to males allowing for age group and time period

Diagnosis	Relative risk	95% Confidence interval
Ependymoma	1.00	0.69–1.45
Adult astrocytoma	1.00	0.71–1.42
Juvenile astrocytoma		
1954–1958	1.61	0.95–2.71
1984–1988	0.60	0.36–1.00
Medulloblastoma		
1954–1958	0.37	0.20–0.71
1984–1988	0.89	0.51–1.56
Other intra-cranial and intra-spinal neoplasms	0.80	0.59–1.08
Neuroblastoma		
1954–1958	0.56	0.33–0.93
1984–1988	1.31	0.80–2.13
Retinoblastoma	0.87	0.60–1.28
Wilms' tumour	1.00	0.76–1.33
Osteosarcoma and chondrosarcoma	1.27	0.85–1.90
Ewing's sarcoma	1.31	0.80–2.16
Rhabdomyosarcoma	0.68	0.47–0.96
Other soft tissue sarcoma	1.01	0.59–1.74
Epithelial neoplasms except skin		
Age <1	*	—
Age 1–4	1.32	0.35–4.91
Age 5–9	0.88	0.27–2.88
Age 10–14	0.57	0.30–1.08
Unspecified malignant neoplasms	0.83	0.48–1.44
All malignant and all central nervous system†	0.84	0.78–0.89

* 3 females, 0 males. † Includes 1407 cases of leukaemia and lymphoma and 26 rare diagnoses.

of clinical services. The Manchester Children's Tumour Registry (MCTR), which was established in 1954 and is population-based, has an ideal data set with which to study incidence patterns. A recent report from the MCTR covering the 35-year period 1954–1988 described patterns and trends in incidence of childhood leukaemia and lymphoma [2]. Statistically significant increases of acute lymphocytic leukaemia, chronic myeloid leukaemia and Hodgkin's disease, but not of acute non-lymphocytic leukaemia or non-Hodgkin's lymphoma were identified. This report presents a parallel analysis of patterns and trends in incidence of childhood solid tumours during the same period, and updates three previous reports from the MCTR which highlighted statistically significant increases, over varying time periods, in incidence of germ cell and epithelial tumours, but not in other groups of solid tumours [3–5]. Also included is an analysis of all childhood malignant disease combined, including the haematopoietic and RE malignancies. A significant increase in incidence of all malignancies was previously observed over the time period 1954–1977 [3].

PATIENTS AND METHODS

The data for this study were extracted from the records of the MCTR which has recorded details of all instances of malignant disease, CNS tumours and certain other neoplastic conditions diagnosed since 1954 in children aged under 15 years and resident in the North Western Regional Health Authority (NWRHA) area at the time of diagnosis. Prior to 1974, the area covered was that of the Manchester Regional Hospital Board (MRHB). A full account of the methods employed by the MCTR was included in the recent report of incidence trends and patterns in leukaemia and lymphoma [2]. Briefly, for each registration, either a detailed abstract or copy of the medical record is stored and, for the vast majority of cases, diagnosis is based on special review of histopathological material. Biopsy material is circulated to a panel of pathologists to ensure diagnostic accuracy and is also stored so that diagnoses can be reviewed.

All cases registered with a malignant or any CNS tumour and diagnosed between 1954 and 1988 were included, except for cases of neuroblastoma found incidentally at postmortem who had no symptoms during life and in whom the neuroblastoma did not contribute to death. Langerhans cell histiocytosis was not included in the analyses.

The data extracted for each registration consisted of sex, age group at diagnosis (<1, 1–4, 5–9, 10–14 years), quinquennia of diagnosis (1954–1958, 1959–1963, 1964–1968, 1969–1973, 1974–1978, 1979–1983, 1984–1988) and diagnostic group. The diagnostic groups, listed in Table 1, were chosen prior to analysis and were based on a classification scheme for childhood cancer [6] with the following modifications applied. Cases of astrocytoma were divided into two groups, optic nerve glioma was combined with juvenile (pilocytic) astrocytoma to form one group, and the remaining cases of astrocytoma formed a second group (hereafter referred to as adult astrocytoma). Both craniopharyngioma and meningioma were separated from the group of miscellaneous intra-cranial and intra-spinal neoplasms and considered individually; the remainder of this group was combined with the group of other gliomas. Other and unspecified malignant renal tumours were included with Wilms' tumour. Osteosarcoma and chondrosarcoma were merged into one group as were the fibromatous and other soft tissue sarcomas. Renal, hepatic and gonadal carcinomas were combined with all the other non-skin epithelial neoplasms to form a group, while carcinoma and melanoma of the skin were combined to form a group of skin tumours. Unspecified hepatic, bone and gonadal tumours were added to the group of unspecified malignant neoplasms. Cases of leukaemia, lymphoma and a few extremely rare diagnoses that did not fall into one of the individual diagnostic groups listed in Table 1 were included in the analysis of all cases.

The cases were tabulated by sex, age group and quinquennia of diagnosis for each diagnostic group using the computer package EPILOG [7]. The MRHB and NWRHA supplied annual mid-year population estimates by sex and age group which were used to estimate person-years at risk tabulated as above. The population estimates were derived from the decennial censuses of England and Wales and adjusted for births, deaths and migration.

Sex-, age group-, quinquennia-specific annual incidence rates per 1 000 000 population were calculated and used to derive summary incidence rates across strata. To account for the change

in childhood age distribution over time, incidence rates for the entire age range were corrected to the world standard population [8]. Rates for the entire time period were similarly corrected by taking a weighted average of the rates within every quinquennium such that the weights used (0.15, 0.15, 0.16, 0.16, 0.14, 0.125, 0.115) were in proportion to the total person-years in the quinquennia. Correction of rates for both sexes combined was unnecessary.

χ^2 tests for heterogeneity between overall rates in sexes and age groups and for heterogeneity and trend over time were carried out [9] providing there were at least 10, 40 and 20 cases, respectively. For tests between rates in time periods, the remaining two factors were controlled for by initially calculating expected numbers within the eight sex/age group strata, using the overall within-strata observed rates, and then summing over strata to obtain total expected numbers. For tests between rates in sexes and in age groups, the expected numbers were calculated similarly.

For every diagnostic group with at least 50 cases and for all cases combined, the effect of sex, age and time period on incidence rates was modelled statistically. It was assumed that the number of cases in a particular sex, age group and time period followed a Poisson distribution, with mean equal to the product of the person-years at risk and annual incidence rate, and that the incidence rate was equal to a product of factors depending upon sex, age group and quinquennia of diagnosis and interactions between these variables, i.e. it was assumed that a log linear model was appropriate for the incidence rates [9]. For each diagnostic group, various models incorporating different factors were fitted to the incidence rates, using the computer package GLIM [10], and the most appropriate model chosen. Temporal changes were of prime interest, and time period effects considered for inclusion in the models were a single change in rates in 1974, a linear trend in which the percentage change in rates per quinquennium was constant, a quadratic effect and complete time heterogeneity. The variation in temporal effects between sexes and age groups was also examined. Initially factors for interactions and main effects were included in the models, and their significance was assessed by the maximum likelihood ratio test. Factors not significant at the 10% level were removed from the model in a stepwise manner, except that if an interaction was retained all lower order interac-

Table 4. Estimates of relative risks in every age group compared to age group with highest incidence rate allowing for sex and time period

	Age group (years)							
	<1		1–4		5–9		10–14	
Diagnosis	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Ependymoma	1	—	0.85	0.49–1.48	0.27	0.14–0.51	0.24	0.12–0.47
Adult astrocytoma	0.28	0.09–0.89	0.62	0.39–0.99	1	—	0.79	0.53–1.18
Juvenile astrocytoma	0.33	0.13–0.82	1	—	0.85	0.60–1.21	0.93	0.66–1.31
Medulloblastoma	0.21	0.07–0.66	0.97	0.68–1.38	1	—	0.43	0.28–0.66
Other intra-cranial and intra-spinal neoplasms								
1954–1958	0.12	0.02–0.72	0.46	0.21–1.00	1	—	0.50	0.24–1.05
1984–1988	2.13	0.91–4.96	0.70	0.35–1.40	1	—	0.57	0.30–1.10
Neuroblastoma	1	—	0.67	0.48–0.93	0.11	0.07–0.17	0.004	0.001–0.029
Retinoblastoma	1	—	0.39	0.26–0.58	0.03	0.01–0.07	0	—
Wilms' tumour	0.93	0.63–1.39	1	—	0.18	0.12–0.26	0.04	0.02–0.09
Osteosarcoma and chondrosarcoma	0	—	0.03	0.01–0.14	0.29	0.18–0.48	1	—
Ewing's sarcoma	0	—	0.21	0.09–0.51	0.68	0.40–1.15	1	—
Rhabdomyosarcoma	0.82	0.44–1.53	1	—	0.45	0.29–0.69	0.35	0.22–0.56
Other soft tissue sarcoma	1	—	0.36	0.15–0.84	0.31	0.14–0.72	0.38	0.17–0.85
Epithelial tumours except skin								
Male	0	—	0.19	0.07–0.56	0.24	0.10–0.57	1	—
Female	1.10	0.32–3.82	0.45	0.16–1.26	0.37	0.13–1.02	1	—
Unspecified malignant tumours	1	—	0.94	0.35–2.50	0.42	0.14–1.22	0.79	0.29–2.11
All malignant and all central nervous system*								
1954–1958	0.73	0.57–0.93	1	—	0.64	0.55–0.75	0.49	0.42–0.58
1984–1988	0.84	0.66–1.08	1	—	0.53	0.45–0.62	0.57	0.49–0.67

* Includes 1407 cases of leukaemia and lymphoma and 26 rare diagnoses.

tions and main effects were automatically included. When no further factors could be eliminated from a model, excluded factors were individually assessed to identify any that might improve the fit. This process was repeated until no further factors could be removed or added. The scaled deviances and residuals obtained from the final models were examined for lack of fit. Maximum likelihood estimates of relative risks (RR) and corresponding 95% confidence intervals (CI) were obtained from the parameters of the models.

RESULTS

Between 1954 and 1988, the MCTR received registrations for 3360 malignant conditions or CNS tumours. Twenty-six were for a specific diagnosis which did not fall into one of the individual diagnostic groups analysed and 1407 for leukaemia or lymphoma which have been described previously [2]; these 1433 cases will not be considered further except in the analysis of all cases. In Table 1, the remaining 1927 cases are shown by diagnosis. One hundred per cent of cases in the majority of diagnostic groups and 93% of cases overall were diagnosed on the basis of biopsy material. The other intracranial and intraspinal neoplasms and the unspecified malignant neoplasms had the smallest percentage of biopsy-proven cases with 103 and 13 cases, respectively, without histological verification. The remaining solid tumours not histologically verified were diagnosed as follows: 12 cases of neuroblastoma and 1 of hepatoblastoma, where the diagnoses were based on biochemistry and radiology reports, and 4 cases of craniopharyngioma, 9 of retinoblastoma, 5 with a renal tumour and 1 of osteosarcoma from radiological and clinical findings.

Patterns and trends in incidence are described below. In Table 1, numbers of cases diagnosed between 1954 and 1988 are shown by age and sex for each diagnosis, together with overall average annual incidence rates and the results of χ^2 tests for heterogeneity. In Table 2, numbers of cases and overall age-corrected average annual incidence rates are shown by quinquennia, together with the results of χ^2 tests for heterogeneity and trend over time. Statistical modelling of the incidence rates was carried out for all groups except craniopharyngioma, meningioma, hepatoblastoma, non-gonadal and gonadal germ cell tumours, and skin cancers. Tables 3–5 show RR estimates and 95% CI, obtained from log-linear modelling, for females relative to males, for each age group relative to that with the highest incidence and for each time period relative to the preceding time period. For each estimate, the remaining two variables have been controlled for. If a RR depends upon the value of another variable, multiple entries appear in the appropriate tables. Figures 1–5 show average age corrected annual incidence rates per 1 000 000 population by time period, sex and diagnostic group and, if applicable, rates predicted by the final models. Evaluation of the final models revealed that the fit was reasonable in all groups with the infrequent exception of an outlying data point. Unless otherwise stated, the results described below are those obtained from log linear modelling rather than χ^2 tests. All time, age and sex effects were considered for inclusion in the models but generally only those actually included in the final model are described.

Table 5. Estimates of relative risks in one time period compared to preceding time period allowing for sex and age group*

Diagnosis	Risk in 5-year time period relative to preceding 5-year time period	
	RR	95% CI
Ependymoma	1.01	0.91–1.11
Adult astrocytoma	1.04	0.95–1.14
Juvenile astrocytoma		
Male	1.15	1.04–1.27
Female	0.98	0.88–1.08
Medulloblastoma		
Male	1.03	0.93–1.14
Female	1.19	1.04–1.36
Other intra-cranial and intra-spinal neoplasms		
Age <1 year	1.75	1.22–2.51
Age 1–4 years	1.15	0.98–1.36
Age 5–9 years	1.08	0.96–1.21
Age 10–14 years	1.10	0.94–1.28
Neuroblastoma		
Male	1.02	0.93–1.12
Female	1.17	1.06–1.30
Retinoblastoma	1.04	0.95–1.15
Wilms' tumour	1.05	0.98–1.13
Osteosarcoma and chondrosarcoma	1.01	0.91–1.12
Ewing's sarcoma	0.96	0.84–1.09
Rhabdomyosarcoma	0.96	0.88–1.05
Other soft tissue sarcoma	1.04	0.90–1.19
Epithelial neoplasms except skin	1.18	1.04–1.35
Unspecified malignant neoplasms	0.21†	0.09–0.49
All malignant and all central nervous system‡		
Age <1 year	1.08	1.01–1.15
Age 1–4 years	1.05	1.02–1.08
Age 5–9 years	1.02	0.98–1.05
Age 10–14 years	1.08	1.04–1.11

* Unless indicated otherwise, estimates obtained from fitting time as a linear trend in log linear model. † Risk in 1974–1988 relative to 1954–1973. ‡ Includes 1407 cases of leukaemia and lymphoma and 26 rare diagnoses.

CNS tumours

Only age had a significant effect on incidence rates of ependymoma and adult astrocytoma (Figure 1); the incidence of ependymoma was greatest in those aged under 5 years and of adult astrocytoma in those aged 5–9 years.

Time trends for juvenile astrocytoma were significantly different between sexes ($\chi^2_1 = 5.026$, $P = 0.03$); in males, there was a significant increasing linear time trend estimated to be 15% per quinquennium, whereas in females there was a non-significant small decreasing linear trend. In contrast, for medulloblastoma, a linear increase in females (estimated to be 19% per quinquennium) was borderline significantly greater than that in males ($\chi^2_1 = 2.84$, $P = 0.09$) (Figure 1). As a consequence of the differential time trends, the estimated RRs in females compared to males changed over the 35-year period. For both juvenile astrocytoma and medulloblastoma, there were signifi-

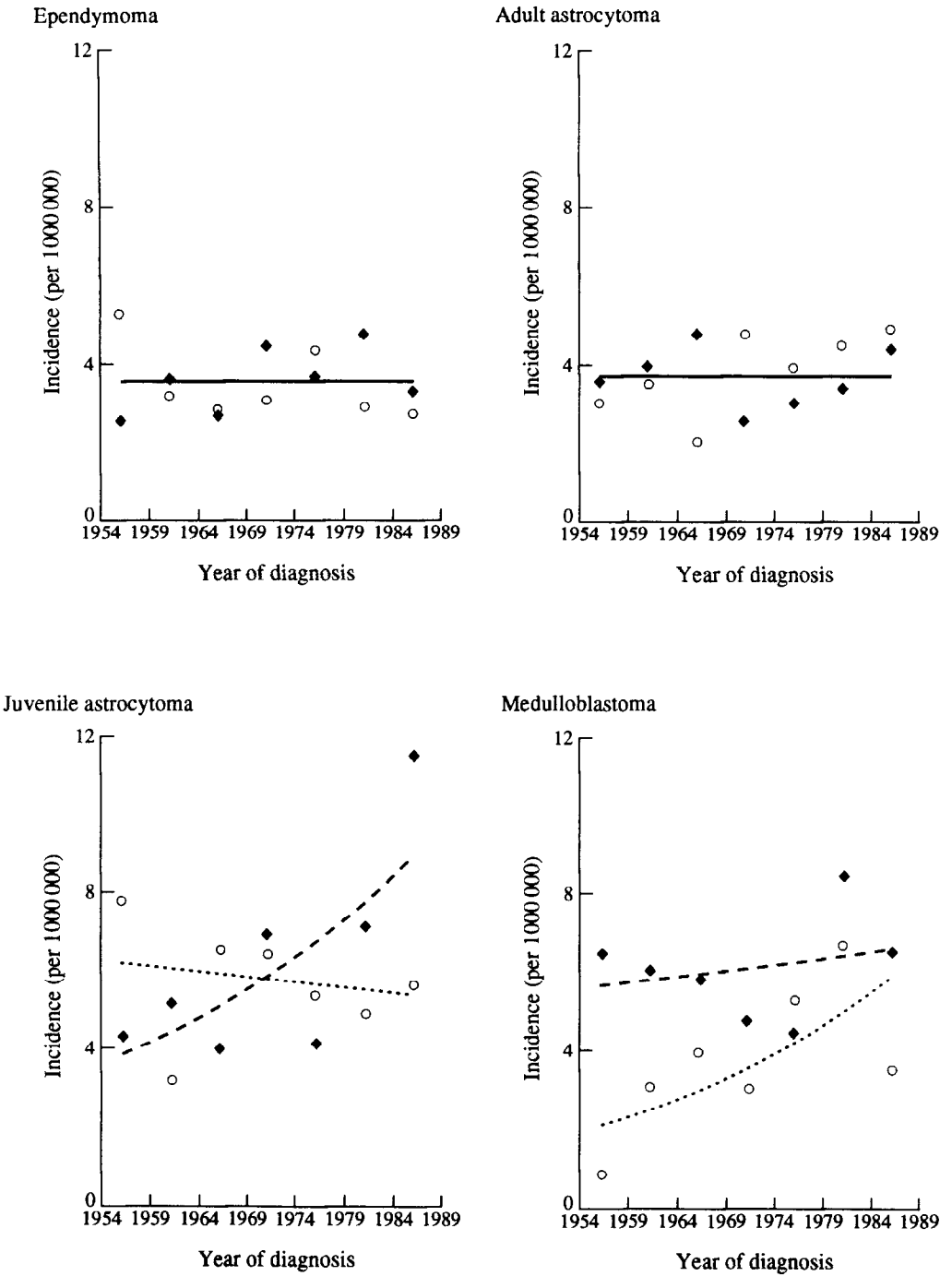

Figure 1. Central nervous system tumours: age-corrected annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence, —— common regression curve for males and females, – – – male regression curve, · · · female regression curve.

cant differences in rates between age groups, but age did not have a significant effect on time trends.

The χ^2 test identified a borderline significant increasing trend for craniopharyngioma, but not meningioma. Neither exhibited a significant difference between sexes, but the incidence of craniopharyngioma varied significantly between age groups.

Incidence rates for the remaining CNS tumours combined changed at significantly different rates between age groups ($\chi^2_3 = 7.80$, $P = 0.05$). The greatest increase was seen in those aged under 1 year, however, this is based on only 12 cases. Increases occurred in both biopsied and unbiopsied tumours. Incidence rates were not significantly different between the sexes.

There was a significant linear increase in the incidence of all CNS tumours combined ($\chi^2_1 = 15.8$, $P = 0.00006$). The estimated increase of 7% per quinquennium (95% CI 4–11%) did not vary significantly by age or sex.

Embryonal tumours

There was a significant difference in time trends of neuroblastoma between sexes ($\chi^2_1 = 3.98$, $P = 0.05$) which was due to a significant linear increase in females estimated as 17% per

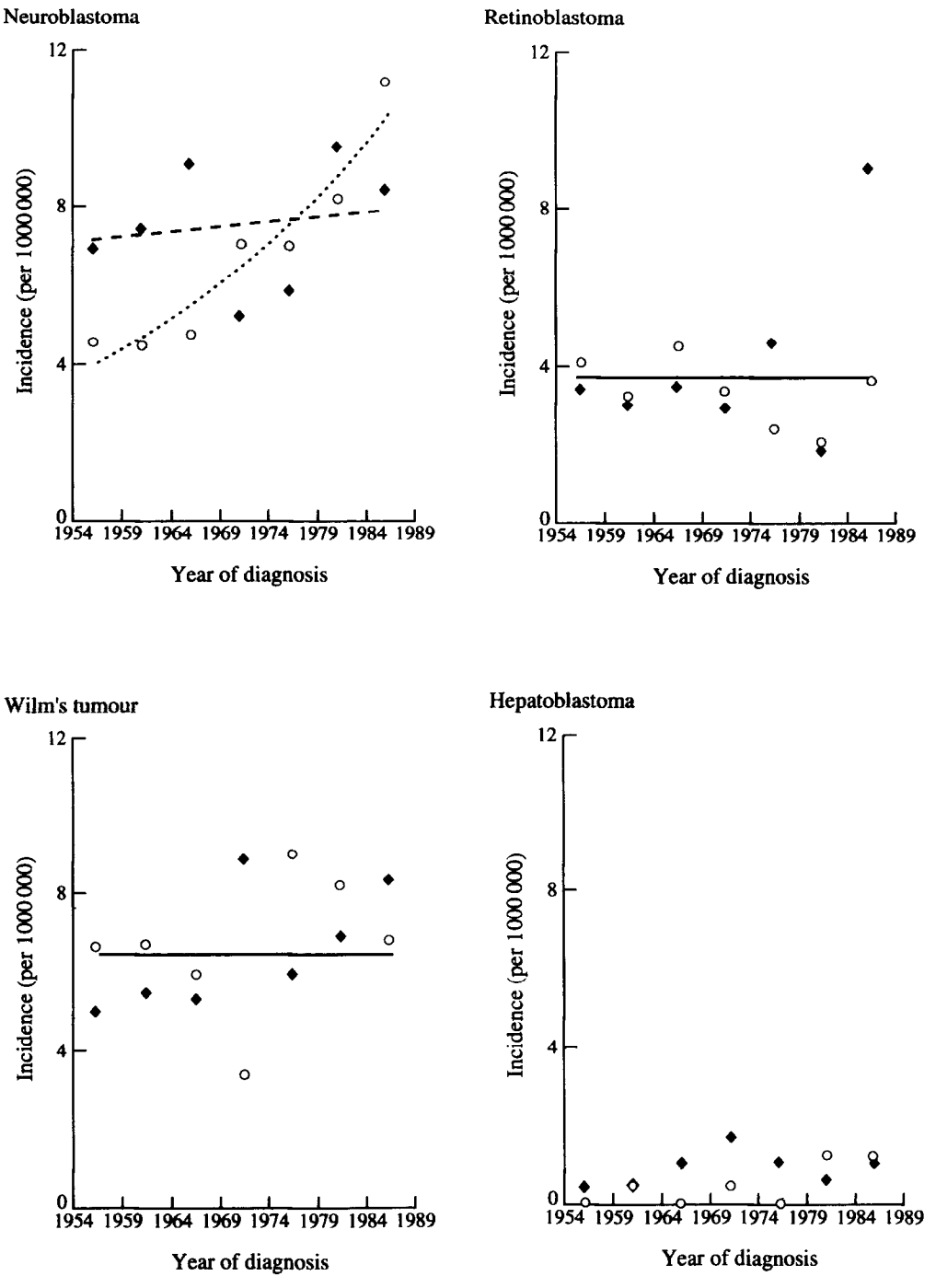

Figure 2. Embryonal tumours: age-corrected annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence, —— common regression curve for males and females, – – – male regression curve, · · · female regression curve.

quinquennium and no significant time trend in males (Figure 2). The estimated RR in females compared to males increased from approximately a half to over 1 during the 35 years. Incidence decreased significantly with age. One observation did not conform to the final model, 7 males aged 5–9 years were diagnosed during the time period 1959–1963 when only 2 would have been expected.

The rates for retinoblastoma and Wilms' tumour did not significantly change over time or differ between sexes, but declined with age (Figure 2). During the final quinquennium, 10 males aged <1 year were diagnosed with retinoblastoma but the final model predicted only 2–3.

χ^2 tests identified both an increase over time and a difference between sexes of borderline significance for hepatoblastoma (Figure 2). Half the total cases and all female cases were diagnosed under 1 year of age.

Bone tumours and soft tissue sarcomas

None of the incidence rates for the groups of bone tumours or soft tissue sarcomas varied significantly over time (Figure 3). The incidence of rhabdomyosarcoma changed significantly with both age and sex. Only age had a significant effect on incidence of bone tumours and other soft tissue sarcomas, for the latter group the effect was of borderline significance only.

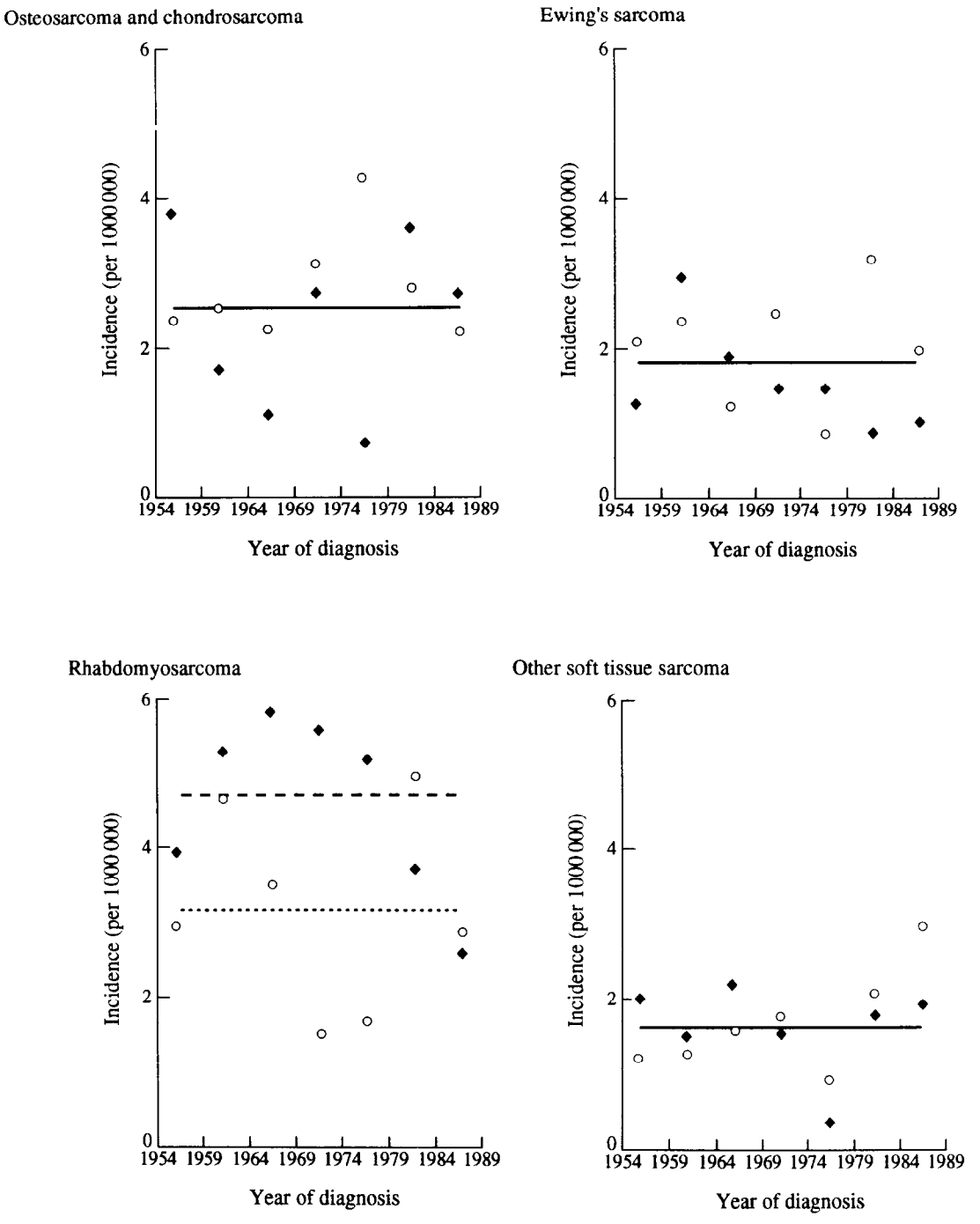

Figure 3. Bone tumours and soft tissue sarcoma: age-corrected annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence, —— common regression curve for males and females, – – – male regression curve, · · · female regression curve.

Germ cell tumours

A significant increase was detected by the χ^2 test in gonadal but not non-gonadal germ cell tumours (Figure 4). For both groups, the age distribution of cases varied between males and females.

Epithelial tumours

The incidence of non-skin epithelial tumours increased significantly over the 35-year period of the study by an estimated 18% per quinquennium (Figure 4). There was a borderline significant interaction between age and sex; incidence increased with age group in males but not in females. Adrenocortical carcinoma mainly accounted for the higher incidence in females than males under age 5 years. Over 5 years of age, the incidence was greater in males than females.

A highly significant increase in the incidence of skin cancers was identified by the χ^2 test (Figure 4).

Unspecified malignant neoplasms

The incidence of unspecified malignant neoplasms was significantly less in the period 1974–1988 than in 1954–1973, the estimated RR in the latter period compared to the former was

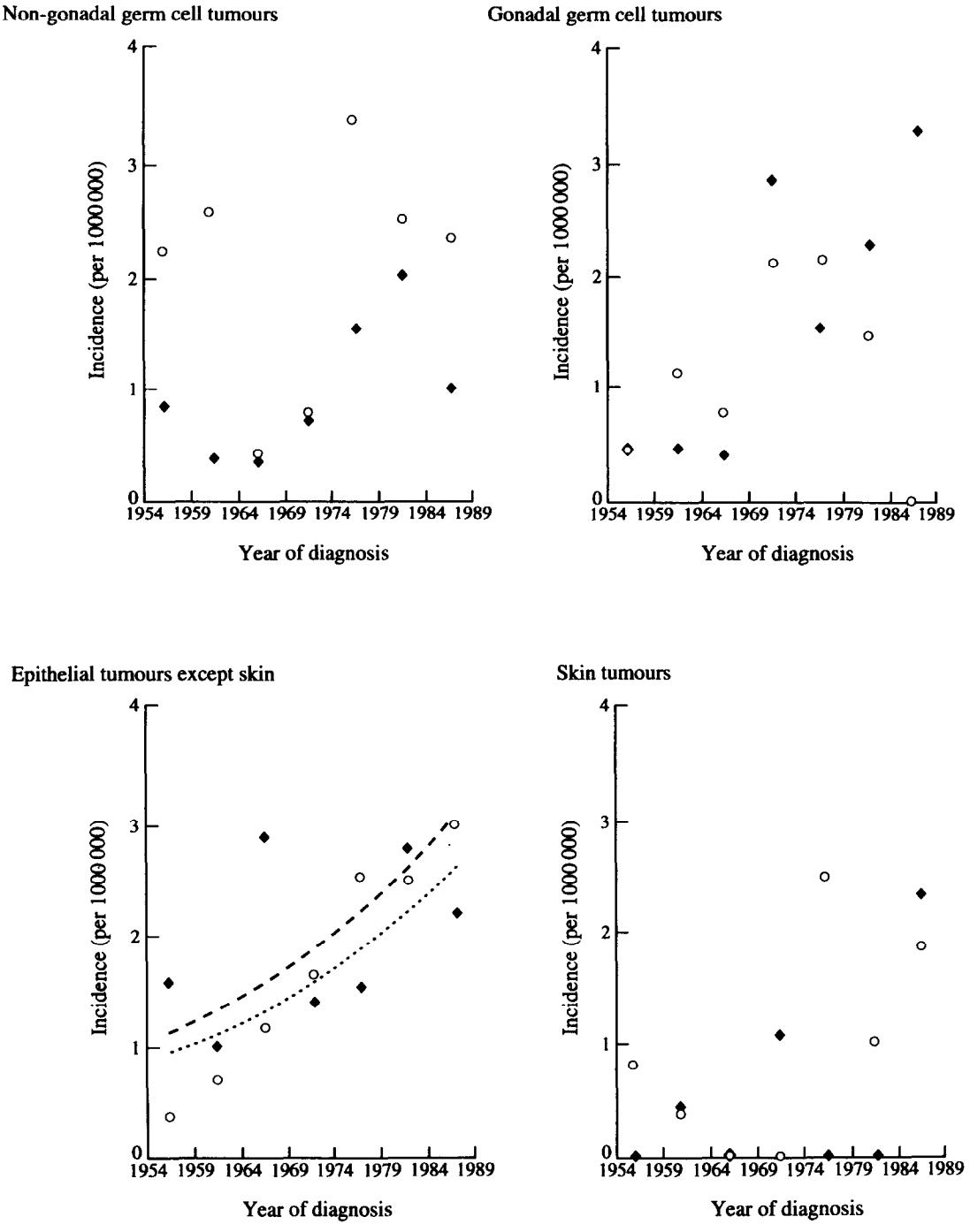

Figure 4. Germ cell and epithelial tumours: age-corrected annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence, – – – male regression curve, · · · female regression curve.

0.21. The model with a single change in rates provided a much better fit to the data than one with a linear decreasing trend. The decline in rates occurred for both biopsied and unbiopsied tumours. Age and sex differences in rates were non-significant.

All malignant and CNS tumours combined

There was a significant linear increase in the incidence of all malignant and CNS tumours combined (including 1407 cases of leukaemia and lymphoma and 26 cases with other rare diagnoses) (Figure 5). The differences between increases in the age groups were of borderline significance ($\chi^2_3 = 6.36, P = 0.09$). In all age groups, except those aged 5–9 years, the estimated increase was significant. Due to the differential time trends, the estimated RRs between age groups changed slightly over the 35 years of the study, but the risk was always at a maximum in those aged 1–4 years. The risk in females was significantly less than in males, but the RR did not vary significantly over time or with age.

DISCUSSION

To study incidence patterns, it is essential that unbiased high levels of ascertainment are achieved and that diagnoses are accurate. If time trends are to be considered, an additional requirement is that all of the above are consistent throughout

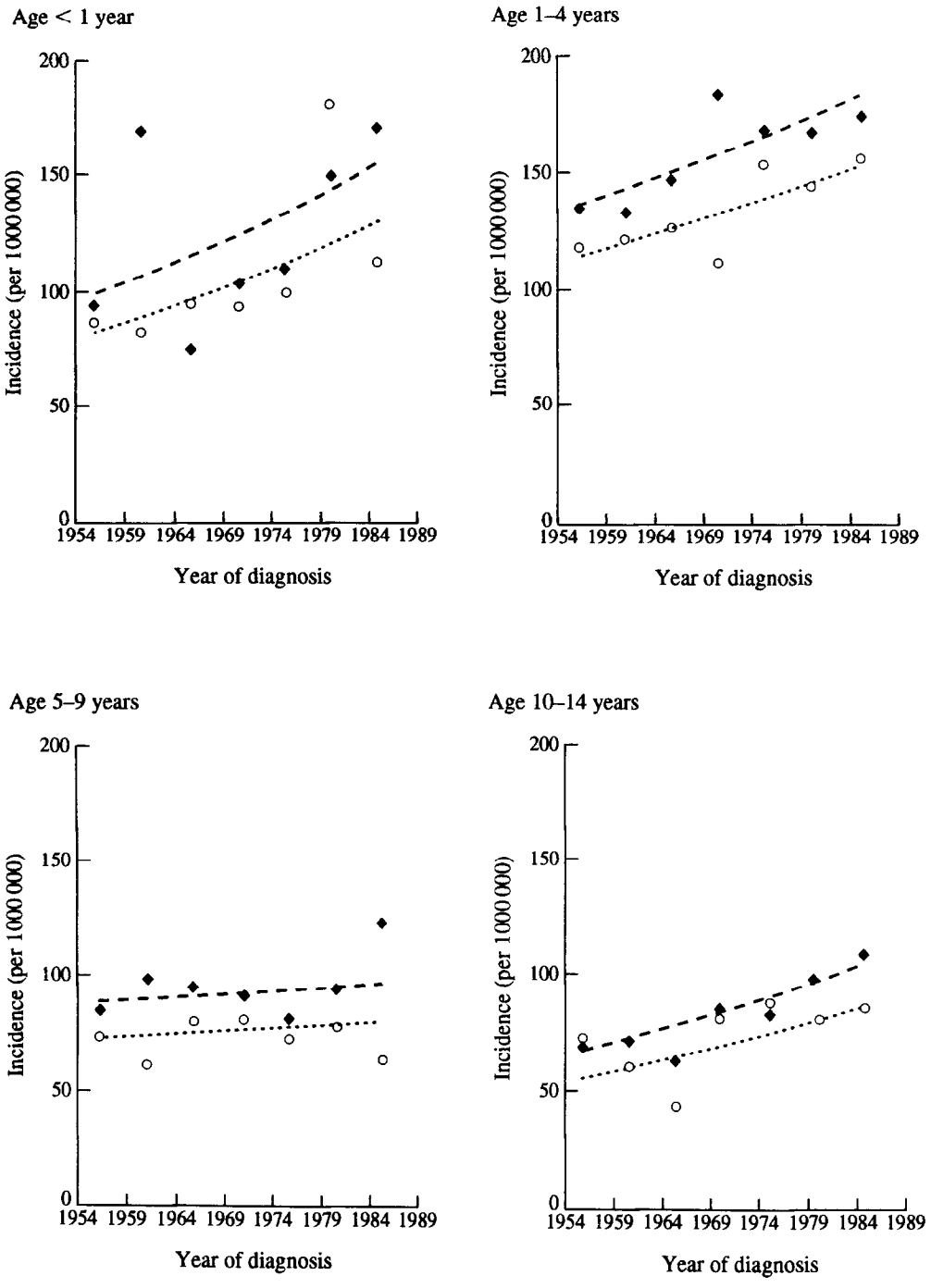

Figure 5. All malignant and central nervous system tumours: age-corrected annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence, – – – male regression curve, · · · female regression curve.

the period under study. During the first 20 years of operation, the MCTR achieved more than 95% complete ascertainment [11] and recent *ad hoc* checks have revealed no reduction from that level. The diagnosis in 93% of cases was histologically verified. Tumour material has been stored by the MCTR for the vast majority of solid tumours since the registry was established in 1954, and is reviewed when new diagnostic techniques become available or when classification systems change. In only two diagnostic groups (other intra-cranial and intra-spinal neoplasms and unspecified malignant neoplasms) were less than 90% of cases histologically verified. In both of these groups, incidence changed significantly over the time period. The increase in other intra-cranial and intra-spinal neoplasms was due to increases in both biopsied and unbiopsied tumours. Improved surgical and radiological techniques during the extended time period of the study may be a component of the former increase. However, this is unlikely to be a major component of the increases in juvenile astrocytoma and medulloblastoma, since significantly different time trends were observed between the two sexes. The increase in unbiopsied tumours could be a consequence of the introduction of computed tomography and magnetic resonance imaging. The decrease in both biopsied and unbiopsied unspecified malignant neoplasms is probably a reflection of improved surgical and biopsy processing techniques, and a greater centralisation

of treatment which occurred during the early 1970s. This decrease does not wholly account for the increased rates seen in some diagnostic groups, since the numbers in this group are small, and there was a significant rise for all cancers combined. The increase in neuroblastoma was restricted to females, and so is unlikely to be a consequence of improved diagnostic techniques. Taking all these points into consideration, it is unlikely that the observed patterns and trends are due to artifacts in the data, with the possible exception of the group of other intra-cranial and intra-spinal neoplasms, for which the results should be interpreted with caution.

In some groups, the power to detect small trends and differential trends between sexes and age groups will be low. This is reflected in the wide CIs for some of the RR estimates. Conversely, log linear models have been fitted to 15 diagnostic groups, so it is possible that some significant effects are due to chance alone.

The previous study from the MCTR covering the period 1954–1977 [3] did not find any significant trends for CNS tumours or neuroblastoma. The differences between the two studies can be reconciled by the fact that, in the earlier study, the sexes were not analysed separately. A change in incidence of unspecified malignant tumours, which occurred around 1974, was probably too late to be identified by the former analysis. Increasing trends in germ cell tumours and epithelial neoplasms previously reported by the MCTR [4, 5] were also observed in this study.

Among childhood solid tumours, incidence trends for the whole of Great Britain have been described only for neuroblastoma and retinoblastoma. An increase of 26% in the age standardised incidence rate of neuroblastoma, for both sexes combined, occurred between 1971–1975 and 1986–1990 [12]. The magnitude of the increase over the 20-year period is compatible with the mean increase for both sexes combined seen in the NWRHA. Retinoblastoma incidence per live birth in Great Britain in the age group 0–4 showed no trend by year of birth from 1962 to 1975, which is in agreement with the present study [13].

An analysis of data from the first four volumes of *Cancer Incidence in Five Continents* (CI5C), covering the period 1958–1977, showed a worldwide increase in childhood brain and CNS tumours, but not in kidney or eye tumours [14]. These results are not directly comparable since CI5C uses a site-based classification. However, they are consistent with the present study.

Studies including time trends in incidence of childhood solid tumours have been reported from several other parts of the world [15–21]. The results for the more common paediatric solid tumours from the larger series are generally consistent with those of this study. An exception was the significant increase seen in Wilms' tumour in Sweden between 1958 and 1974 [16]. Analogous to the present study, in Connecticut and Sweden, a greater increase in neuroblastoma was exhibited in females than in males, although these differences were not statistically assessed [15, 16]. None of these other studies has the extensive and accurate diagnostic information from which the present study benefits. The age–sex patterns in incidence seen in this study are compatible with those in other Caucasian populations [1, 12, 13, 15–19, 21–26].

The long series of case data and histopathology material held by the MCTR has enabled time trends, thought to be independent of improvements in diagnostic methods and ascertainment etc., to be recognised for some diagnostic groups. It is unlikely that aetiological factors common to all diagnostic groups, in which increases in incidence have been observed, are operating. For example, in embryonal and germ cell tumours diagnosed during the first 5 years of life, it is likely that prenatal, including genetic, factors are important. Conversely, among the epithelial tumours which occur predominantly in older children, environmental factors acting postnatally may be more important. It is, however, worth noting that in Wilms' tumour, retinoblastoma, rhabdomyosarcoma and osteosarcoma, where germ line mutations in tumour suppressor genes are known to be involved in a proportion of the cases, no trends in incidence with time were observed. Further work is now required to identify specific aetiological factors.

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Science Papers

Parallel Studies of Clonogenic Leukaemia Cells and the Leukaemia Cell Population as a Whole in Acute Myelogenous Leukaemia

H.D. Preisler, S.D. Banavali, M. Yin, G. Venu, Y.Q. Li, F. Gaskins and A. Raza

The clonogenic cells in patients with acute myelogenous leukaemia (AML) were evaluated with respect to the relationship between primary and secondary cloning capacity and the proliferative and molecular biological characteristics of the leukaemia cell population as a whole. Secondary cloning capacity was correlated with primary cloning efficiency, and with the ability of the clonogenic cells to produce large sized clones. The cloning capacity of AML cells was unrelated to the cell cycle characteristics of the leukaemia cell population *in vivo* or to the level of myc, myb, fms, or interleukin (IL)1β expression. The sensitivities of the clonogenic cells to cytosine arabinoside and daunorubicin were inversely correlated with the ability of the leukaemia cells to produce large sized clones *in vitro*. This latter observation may explain the reported relationships between the clonogenic capacity of AML cells and response to chemotherapy.

Key words: acute myeloid leukaemia, clonogenicity, primary cloning efficiency, secondary cloning efficiency, cell cycle characteristics, drug sensitivities, MYC, MYB
Eur J Cancer, Vol. 30A, No. 10, pp. 1511–1516, 1994

INTRODUCTION

HUMAN ACUTE myelocytic leukaemia (AML) cells, capable of clonogenic growth *in vitro*, represent a sub-population of cells whose properties appear to differ from that of the leukaemia cell population as a whole. The clonogenic cells have a more immature immunophenotype than that of the population as a whole [1], and the clonogenic subpopulation has a higher proportion of cells in S-phase than the leukaemia population as a whole [2]. While all clonogenic cells are CD34+, not all CD34+ AML cells are clonogenic *in vitro* [3, 4]. Additionally, the demonstration that some of the clonogenic AML cells have the capacity to 'self renew' suggests that, even within the clonogenic cell population, there are sub-populations with different proliferative capacities [5, 6].

The study described here was conducted to investigate the possible relationships between the characteristics of the leukaemia cell populations as a whole and the clonogenic cells.

PATIENTS AND METHODS

Patients and preparation of cells

This study consisted of specimens obtained from 43 patients with AML. Informed consent was obtained from each patient. Forty-seven bone-marrow (BM) and 46 peripheral blood (PB)

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