 International Journal of Epidemiology 2001;**30**:1428–1437

Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers

John D Dockerty,[a,b] Gerald Draper,[a] Tim Vincent,[a] Steve D Rowan[c] and Kathryn J Bunch[a]

Background	Parental ages, parity, and social class have been found in some studies to be associated with particular childhood cancers. Further investigation is warranted because of conflicting findings, biases, and the need to test specific hypotheses.
Methods	A case-control study was conducted (England and Wales, ages 0–14 years). Cases were ascertained from the National Registry of Childhood Tumours, and were born and diagnosed during 1968–1986. Birth record controls were matched 1:1 to cases on date of birth, sex and area. Information on variables of interest for both groups came from birth records. In all, 10 162 pairs could contribute to matched analyses.
Results	The odds ratio (OR) for retinoblastoma resulting from assumed new germ cell mutations among children of fathers aged ⩾45 years was 3.0 (95% CI : 0.2–41.7). The risk of childhood acute lymphoblastic leukaemia (ALL) was significantly higher among children of older mothers and fathers, and significant trends with increasing mothers' ($P < 0.001$) and fathers' ($P = 0.002$) ages were found. There was a strong and significant protective effect of increasing parity on risk of childhood ALL. The adjusted OR for parity of ⩾5 (versus 0) was 0.5 (95% CI : 0.3–0.8). Children in more deprived communities had a lower risk of ALL; but this was not significant after confounders were allowed for. There was no significant effect of social class based on parental occupation on ALL risk, but the numbers were small in those analyses.
Conclusions	The associations between ALL and parental ages did not disappear when children with Down syndrome were excluded, suggesting an additional explanation beyond known links. The strong ALL association with parity may be because of an unknown environmental risk factor.

Keywords	Child, cancer, leukaemia, retinoblastoma, parental age, parity, social class, case-control, risk
Accepted	21 May 2001

Family structures have changed dramatically in the past four decades.[1] Children born in the 1990s are more likely to be born to older mothers and to have fewer siblings than was the case for their parents.[1] Having an older mother or father may increase the risk of some health problems in a child;[2,3] one theoretical consequence is an increased risk of certain childhood cancers. Different effects might be expected depending on whether it is the mother or father who is older, although often it is both. Older mothers are more likely to have children with trisomies, including of chromosome 21.[2] Children with Down syndrome have an increased risk of childhood leukaemia, with relative risk estimates mostly between 10 and 30.[4] The increased risk is found for both acute lymphoblastic leukaemia (ALL) and acute non-lymphoblastic leukaemia (ANLL).[4]

Older fathers (but not older mothers) may be more likely to have children with new inheritable-mutation disorders.[2] Some childhood cancers are associated with a known or strongly suspected inherited predisposition. One might therefore expect there to be an increased risk of such cancers among the offspring of older fathers, but not (except indirectly) older mothers.[5]

[a] Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, 57 Woodstock Road, Oxford OX2 6HJ, UK.

[b] Department of Preventive and Social Medicine, University of Otago, PO Box 913, Dunedin, New Zealand.

[c] Office for National Statistics, 1 Drummond Gate, London SW1V 2QQ, UK.

Correspondence: Dr John Dockerty, Department of Preventive and Social Medicine, University of Otago, PO Box 913, Dunedin, New Zealand.

Bilateral retinoblastoma with no previous family history is the best example of this type of tumour.[5]

Some early studies showed an increased risk of childhood leukaemia for firstborn children, but several subsequent studies have not confirmed this.[6,7] Associations with birth order or parity may be relevant to hypotheses of an infective aetiology for childhood leukaemia.[8–10] Kinlen[9] suggested that childhood leukaemia occurs as a rare response to a common infection, and that population influxes into rural areas with higher proportions of susceptible individuals favour the occurrence of epidemics of the infection, and increases in leukaemia incidence. Kinlen and others have tested this hypothesis, mainly through ecological studies of such 'population mixing' in relation to the occurrence of childhood leukaemia. Excesses of childhood leukaemia have been found in a variety of situations where population mixing has occurred.[9,11] Greaves[8] suggested that the risk of the common B-cell precursor subtype of ALL was increased by certain general patterns of infection—notably delayed or diminished exposure to infections in infancy. Firstborn children may experience delayed exposure to common infections in infancy, and it has been suggested that the increased risk of leukaemia found for firstborn children in some studies lends support to Greaves' hypothesis.[8] In data from England, Wales and Scotland 1971–1984, there was an early age peak in the incidence of childhood ALL at ages 2–3 years, and the incidence was higher at ages 1–5 than at ages under 1 or 6–14 years.[12] Childhood leukaemia occurring around the age of peak incidence is usually the common variant of B-cell precursor ALL.[13] In relation to Greaves' hypothesis, it may be useful to consider children with ALL at ages 1–5 years separately when assessing risk factors that may be associated with variations in exposure to infection, such as parity and social class.

An increased risk of childhood leukaemia in relation to high socioeconomic level has been reported in studies from several countries including Britain.[6,14] However, this has not always been found.[15] It is possible that the associations with areas of high socioeconomic level observed in some UK ecological studies might not apply at the individual level. To infer that they do might be an example of the ecological fallacy. Misclassification can also occur in case-control or cohort studies that use grouped data to assign characteristics to individuals (e.g. assigning the average social class of a group of people in an area to an individual living in that area).[16,17] Thus, incorrect inferences could occur in both ecological and analytical studies of childhood cancer as a result of using characteristics of groups (e.g. census data for particular areas) rather than characteristics of individuals to assign socioeconomic levels. Although parental ages, parity and socioeconomic level may relate to different aetiological pathways for childhood cancers, it is sensible to consider them together because they are inter-related and this has implications for multivariate modelling. The biological hypotheses examined in this study were:

(1) That children of older fathers (⩾45 years) are at increased risk of retinoblastoma due to new paternal germ cell mutations. No increase in risk is expected among children of older mothers because of maternal age alone.
(2) That there is an increasing risk of childhood ALL and ANLL with increasing maternal age, but this is due to associations with Down syndrome.
(3) That firstborn children have a higher risk of childhood ALL and ANLL.
(4) That in the UK, high socioeconomic level is associated with an increased risk of childhood ALL and ANLL when it is assigned using averaged data from communities, but not when it is based on specific data for individual families (e.g. parental occupation).

In this paper, a new paternal germ cell mutation is assumed to have occurred if retinoblastoma is bilateral and/or the only affected relatives are descendants. Familial risks are recognized for some cancers other than retinoblastoma. Examples include Wilms' tumours, neuroblastomas, central nervous system (CNS) tumours (e.g. in neurofibromatosis), and soft tissue sarcomas (e.g. in Li-Fraumeni syndrome).[6,18] However, we would not expect to be able to detect paternal age effects for these tumours. This is because the proportion of familial cases is small and we cannot easily identify new heritable mutations.

Materials and Methods

Case ascertainment and control selection

The cases were obtained from the British National Registry of Childhood Tumours (NRCT). This includes childhood cancer deaths since 1953 and registrations since 1962.[19] For leukaemias and non-Hodgkin's lymphomas, completeness of ascertainment was estimated to be about 99% for the period 1969–1983.[20] Diagnostic accuracy is thought to be high.[19] During the study period (1968–1986), 91% of the registrations were based on histology.

Cases in the present study were born in England or Wales between 1968 and 1986 and diagnosed with any malignancy at age 0–14 years in the same time period. Children born in 1981 were excluded, because the required data were incomplete as a result of birth registration difficulties affecting that year. Adopted children were also excluded. Diagnoses were classified according to the International Classification of Childhood Cancer.[21] Within the leukaemias, we distinguished acute lymphoblastic and acute non-lymphoblastic. Benign CNS tumours were included.

In a previous study, controls had been selected at random from birth entries held on the Office of Population Censuses and Surveys (OPCS, now Office for National Statistics [ONS]) England and Wales birth registers.[22] There was 1:1 matching to cases on date of birth (within 6 months), sex, and birth registration sub-district. Details are given elsewhere.[22] If either the case or the control was born in 1981, both members of the matched pair were excluded.

Variables of interest

Draft birth entries for children born in England and Wales are held by the OPCS, whose staff found and copied the birth entries of cases using identifying information from the NRCT. The OPCS staff also selected the controls from the birth registers, following specified procedures.[22] Birth entry information was then used to obtain the full electronic birth record of each case and control held by the OPCS. Access to some data (e.g. parental dates of birth) is restricted by legislation; hence the analyses were done at the ONS.

The following information was sought from the birth record of each case and control: sex and date of birth of the child,

date of birth registration, parents' years of birth and ages at the time of the child's birth, whether the birth was within or outside marriage, parity (the total number of previous children live born and stillborn to the mother), 'parental social class' (almost always father's) and mother's usual place of residence at the time of the child's birth (hereafter referred to as birth address). Children born outside marriage were excluded because there were differences in the way some birth data were recorded in relation to marital status.[23] Importantly, numbers of live born and stillborn children (and hence parity) were only available on the birth records of children born within marriage. Because of this, if either member of a case-control pair was born outside of marriage, we excluded both members of the pair. For the period covered by this study, this affected a small proportion of the total—the numbers are given in the next section of Methods. For cases and controls born within marriage, parity data only included previous live or stillborn children by the present or any former husband. Social class of the working parent was allocated based on the Standard Occupational Classification.[24]

For cases only, some information was available from the NRCT about whether they had Down syndrome. We could also say whether retinoblastomas were likely to be 'sporadic unilateral', 'assumed old germ cell mutations' or 'assumed new germ cell mutations'. These categories were based on laterality and family history. Bilateral cases are virtually always heritable. Unilateral cases are usually sporadic, but some will be heritable, reflecting incomplete genetic penetrance. The classification of unilateral cases as 'sporadic' and of heritable cases as 'old' or 'new' germ cell mutations depends on the completeness of family histories and on linkages made between family members at the NRCT. Taking into account the various possibilities for error, the proportions misclassified seem likely to be small.

Proportions of cases and controls with data available

There were 13 739 cases born in England and Wales during 1968–1986 and diagnosed in the same time period with any malignancy or benign CNS tumour. Information on these was sent to the OPCS, and the birth entries were found for 13 373 (97.3%). The remainder included 139 not traced, 140 born abroad and 87 adopted. A control was selected for each of the 13 373 cases, and thus 26 746 records were sent for matching to the computerized birth primary files containing the full electronic birth records. There was successful matching for 26 337 (98.5%). Among these were 93 individual records for which the corresponding case or control had not been matched. These 93 were removed, along with a further 502 case-control pairs for whom at least one member of the pair was born in 1981. This left 25 240 individuals (12 620 pairs). A further 1752 pairs (13.9%) were excluded because one or both members of the pair were born outside marriage, leaving 10 868 case-control pairs. Those with missing data on any of mother's age, father's age or parity (Table 2) were excluded (86 cases and 82 controls, representing 112 pairs), leaving 10 756 pairs.

A deprivation score, calculated according to Carstairs and Morris' method,[25] was used in the analyses together with its four component measures (overcrowding, male unemployment, low social class and no car). Deprivation scores were assigned to individuals but were based on ecological information about the census wards corresponding to the birth addresses. The birth addresses were assigned to postcodes, and these to 1981 census wards. The 1981 census was the closest to the middle of our study period. Temporal changes in the deprivation scores of some wards may have occurred, but across the whole study we would not expect such changes to have been very different for cases and controls. As shown in Table 2, there were 221 cases (2.0%) and 391 controls (3.6%) who could not be given scores because their birth addresses could not reliably be allocated to 1981 wards. The lower proportion of cases reflects the fact that the birth addresses were postcoded before we initiated this study, and address information was more likely to have been available for cases than for controls. This situation could not be ameliorated for this study. The small percentage difference in proportions not coded indicates that this difference between cases and controls would not have caused important bias. Overall, 594 pairs were excluded because of missing deprivation scores, leaving 10 162 pairs (across all diagnoses) that could contribute to matched analyses.

No births in 1968–1972 in the source data set were coded for social class. For 1973–1986, (excluding 1981) only a proportion of births nationwide was coded (13.2% in our data set). The exact proportion coded was different for different birth years,[26] but there should have been no systematic difference in the coding of cases and controls. Overall in this study, social class was available for only about 7% of cases and 6% of controls (Table 2).

Analyses

Categories for variables were set before the case-control analyses were carried out. The main method of analysis was conditional logistic regression.[27] The confounder variables included are listed in the footnotes of the Tables of results. Unconditional (unmatched) logistic regression was used for the analyses of social class based on parental occupation; because of the amount of missing data; if just one member of a matched pair had missing data, only that individual case or control was excluded. The child's birth registration year (grouped) and sex were always adjusted for when the matching was broken.

Parental ages were modelled as age group categories, and also as individual years of age to assess trends. In the latter, the result is the odds ratio (OR) that occurs when the age changes by one year. The same approach was taken with the other variables, to produce OR for categories (e.g. for deprivation score), and an OR for the effect of a change in each variable by 1 unit. For the latter, linear trends were assessed in logistic regressions that modelled levels of categorical data as continuous variables. Parental age analyses were conducted for major diagnostic categories of the International Classification of Childhood Cancer[21] and some subgroups (see Results). Analyses for parity and socioeconomic variables were conducted for ALL (ages 0–14 and 1–5 years) and ANLL (ages 0–14 years). Age at diagnosis was known for each case child. For the analyses restricted to ages 1–5 years, controls were included if the age at diagnosis for the matched case child was in this age range.

Results

The distribution of children with cancer by age, sex and diagnostic group is shown in Table 1. Table 2 shows cases and controls by parental ages, parity, deprivation and social class.

Table 1 Background characteristics of the children with cancer

Characteristic	Categories	No. of cases	Per cent of total
Age (years)	<1	1300	12.0
	1–4	5037	46.3
	5–9	2849	26.2
	10–14	1682	15.5
Sex	Boy	6113	56.2
	Girl	4755	43.8
Diagnosis	I. Leukaemias (total)	3878	35.7
	Acute lymphoblastic[a]	3153	29.0
	Acute non-lymphoblastic[a]	563	5.2
	Other and unspecified[a]	162	1.5
	II. Lymphomas & other reticuloendothelial neoplasms	932	8.6
	III. CNS and misc. intracranial & intraspinal neoplasms	2339	21.5
	IV. Sympathetic nervous system tumours (total)	812	7.5
	IVa. Neuroblastoma & ganglioneuroblastoma	799	7.4
	V. Retinoblastoma (total)	415	3.8
	i Sporadic unilateral[b]	228	2.1
	ii Assumed old germ cell mutation[b]	65	0.6
	iii Assumed new germ cell mutation[b]	119	1.1
	iv Unknown	3	0.0
	VI. Renal tumours	780	7.2
	VIa. Wilms' tumour, rhabdoid and clear cell sarcoma	771	7.1
	VII. Hepatic tumours	100	0.9
	VIII. Malignant bone tumours	367	3.4
	IX. Soft tissue sarcomas	672	6.2
	X. Germ cell, trophoblastic & other gonadal neoplasms	335	3.1
	XI. Carcinomas & other malignant epithelial neoplasms	207	1.9
	XII. Other & unspecified malignant neoplasms	31	0.3
Total		10 868	100.0

[a] Down syndrome was recorded among 55 of the 3153 children with ALL (1.7%), 39 of the 563 children with ANLL (6.9%), and 9 of the 162 children with other or unspecified leukaemias (5.6%). No information was available on Down syndrome among the controls, but it seems reasonable to assume that the occurrence would reflect that in the base population during the period covered.

[b] See Methods for an explanation of the sub-categories of retinoblastoma.

Main findings relevant to the study hypotheses

The OR for retinoblastoma resulting from assumed new germ cell mutations among children of fathers aged ⩾45 years was raised, but not statistically significant. Risk estimates did not increase continuously with increasing father's age (Table 3). For this group of case children, there was also a higher OR for the highest category of maternal age; this too was non-significant, although there was some evidence of a trend ($P = 0.03$). Overall, we did not find statistically significant evidence to support a paternal age effect, and we did not find a complete absence of effect in relation to maternal age. The latter may be partly because of the correlation of father's and mother's ages (see later).

The risk of ALL was significantly higher among children of older fathers and mothers, and significant trends with increasing parental ages were found (Table 3). Associations with Down syndrome did not fully explain the associations between childhood ALL and older parental ages. There were no statistically significant trends for ANLL in relation to parental ages.

There was a very strong association between parity and the risk of childhood ALL (Table 4). Greater parity was protective. There was a significant trend and the effect was more marked among those aged from 1–5 years at diagnosis than across the whole childhood age range. Adjustment for deprivation score made little difference to the OR, but when maternal age was included in the multivariate models the effect of parity became more pronounced and statistically more significant (Table 4). Parity was not related to the risk of childhood ANLL.

Those who lived in more affluent communities had a higher risk of ALL, although the 'protective' effect of deprivation score diminished and was not statistically significant when maternal age and parity were adjusted for as confounders (Table 5). The results for deprivation score were very similar to those for three of its components (unemployment, overcrowding, and car ownership; not tabulated). The results for the other component (proportion in lower social classes) were a bit more marked and statistically significant both before and after adjustment for confounders

Table 2 Distribution of variables of interest among case and control children

		Cases		Controls	
Characteristic	**Categories**	No.	%	No.	%
Mother's age (years)	<20	732	6.7	793	7.3
	20–24	3559	32.7	3646	33.5
	25–29	3830	35.2	3811	35.1
	30–34	1829	16.8	1797	16.5
	35–39	651	6.0	615	5.7
	40+	185	1.7	132	1.2
	Missing data[a]	82	0.8	74	0.7
Father's age (years)	<20	218	2.0	224	2.1
	20–24	2305	21.2	2386	22.0
	25–29	3877	35.7	3903	35.9
	30–34	2574	23.7	2462	22.7
	35–39	1165	10.7	1181	10.9
	40–44	427	3.9	433	4.0
	45+	237	2.2	207	1.9
	Missing data[a]	65	0.6	72	0.7
Parity	0	4410	40.6	4397	40.5
(The total no. of live	1	3781	34.8	3752	34.5
born and stillborn	2	1584	14.6	1577	14.5
children previously	⩾3	1032	9.5	1080	9.9
borne within marriage)	Missing data[a]	61	0.6	62	0.6
Deprivation score	1st fifth (most affluent)	1544	14.2	1521	14.0
(Carstairs and Morris)	2nd fifth	1624	14.9	1542	14.2
	3rd fifth	1761	16.2	1740	16.0
	4th fifth	2345	21.6	2330	21.4
	5th fifth (most deprived)	3373	31.0	3344	30.8
	Missing data	221	2.0	391	3.6
Social class	I or II	239	2.2	196	1.8
	IIIN or IIIM	391	3.6	333	3.1
	IV or V	166	1.5	142	1.3
	Not classifiable or other	31	0.3	19	0.2
	Not coded (missing—see Methods)	10 041	92.4	10 178	93.7
Total		10 868	100.0	10 868	100.0

[a] There were 61 cases and 62 controls who had mother's age, father's age and parity all missing.

(Table 5). It should be noted that the value for 'the proportion in the lower social classes' assigned to each ward is based upon only about a 10% sample of the households in that ward. There were no associations between childhood ANLL and deprivation.

In Table 6 (unmatched analyses) ALL and ANLL risks are shown in relation to the social class of the individual based on paternal occupation. This variable was only available for a much reduced sample size. For ALL with 219 cases and 215 controls, there was no significant effect of individual social class, although there was a suggestion from the point estimates that those in social class I or II may have a higher risk. Interpretation of the ANLL results in Table 6 is hampered by the very small numbers of cases and controls.

Other findings, additional to the specified hypotheses

Table 3 is limited to diagnostic groups of interest: i.e. ALL, ANLL and retinoblastoma. For one other diagnostic group that is not in the Table, there was a significant trend with parental age. This was malignant bone tumours, for which the risk increased with increasing maternal age (trend analysis OR = 1.06, $P = 0.002$), but the categories with higher point estimates of risk were ages 30–34 (OR = 1.8) and 35–39 (OR = 2.3) rather than the highest category of ⩾40 years (OR = 1.2). There was no clear pattern between bone tumour risk and father's age.

Issues related to correlations between variables and confounding

Mother's and father's ages are correlated to the extent that it is impossible to completely disentangle them. When father's age was fitted to the ALL model after mother's age was already in, there was little improvement in the fit (the deviance changed little). There was a greater impact of the reverse procedure (i.e. of adding the mother's age to a model with the father's age already in), but the fit still did not improve to any important

Table 3 Odds ratios for childhood cancers of interest by maternal and paternal ages (conditional logistic regression)

	Adjusted[a] odds ratio (CI[b]) for parental age						
	Maternal age						
Tumour	<20	20–24	25–29[c]	30–34	35–39	40+	Trend analysis[d]
Ia. Acute lymphoblastic leukaemia (total)	1.00 (0.80–1.24)	0.91 (0.80–1.03)	1.00	1.08 (0.93–1.26)	1.40 (1.10–1.78)	1.97 (1.23–3.15)	1.03, $P < 0.001$ (1.01–1.04)
ALL excluding cases with Down syndrome and their matched controls	1.02 (0.81–1.27)	0.90 (0.79–1.02)	1.00	1.05 (0.90–1.23)	1.30 (1.01–1.66)	1.88 (1.17–3.04)	1.02, $P < 0.001$ (1.01–1.03)
Ib. Acute non-lymphoblastic leukaemia (total)	0.94 (0.53–1.66)	0.89 (0.65–1.22)	1.00	0.65 (0.44–0.96)	0.86 (0.50–1.46)	3.07 (0.97–9.75)	1.00, $P = 0.91$ (0.98–1.03)
ANLL excluding cases with Down syndrome and their matched controls	0.98 (0.54–1.75)	0.93 (0.68–1.29)	1.00	0.60 (0.40–0.91)	0.86 (0.49–1.52)	2.04 (0.60–6.89)	0.99, $P = 0.59$ (0.97–1.02)
V. Retinoblastoma (total)	0.84 (0.45–1.59)	0.75 (0.53–1.08)	1.00	1.34 (0.88–2.05)	1.08 (0.58–2.01)	1.30 (0.32–5.26)	1.03, $P = 0.07$ (1.00–1.07)
i Sporadic unilateral	1.26 (0.51–3.08)	0.85 (0.53–1.37)	1.00	1.09 (0.60–1.97)	1.00 (0.45–2.21)	0.57 (0.09–3.76)	1.00, $P = 0.92$ (0.96–1.05)
ii Assumed old germ cell mutation	0.55 (0.11–2.69)	0.80 (0.28–2.26)	1.00	1.68 (0.47–6.01)	1.18 (0.17–8.06)	–[e]	1.07, $P = 0.23$ (0.96–1.19)
iii Assumed new germ cell mutation	0.82 (0.21–3.14)	0.59 (0.28–1.25)	1.00	2.03 (0.87–4.74)	1.55 (0.37–6.43)	4.19 (0.31–56.7)	1.08, $P = 0.03$ (1.01–1.16)

	Paternal age							
	<20	20–24	25–29[c]	30–34	35–39	40–44	45+	Trend analysis[d]
Ia. Acute lymphoblastic leukaemia (total)	1.03 (0.70–1.51)	0.94 (0.81–1.09)	1.00	1.07 (0.93–1.23)	1.10 (0.92–1.32)	1.45 (1.10–1.92)	1.54 (1.06–2.23)	1.02, $P = 0.002$ (1.01–1.03)
ALL excluding cases with Down syndrome and their matched controls	1.04 (0.71–1.52)	0.94 (0.81–1.09)	1.00	1.06 (0.92–1.22)	1.07 (0.90–1.29)	1.36 (1.02–1.81)	1.52 (1.04–2.21)	1.01, $P = 0.007$ (1.00–1.02)
Ib. Acute non-lymphoblastic leukaemia (total)	0.75 (0.34–1.69)	1.30 (0.91–1.85)	1.00	1.02 (0.73–1.43)	1.13 (0.72–1.76)	1.37 (0.74–2.55)	1.23 (0.47–3.23)	1.00, $P = 0.98$ (0.98–1.02)
ANLL excluding cases with Down syndrome and their matched controls	0.86 (0.36–2.04)	1.29 (0.90–1.86)	1.00	1.00 (0.71–1.42)	1.04 (0.66–1.66)	1.32 (0.68–2.56)	1.59 (0.57–4.42)	1.00, $P = 0.84$ (0.97–1.02)
V. Retinoblastoma (total)	1.09 (0.43–2.77)	0.64 (0.42–0.97)	1.00	1.33 (0.88–2.00)	0.91 (0.55–1.52)	0.82 (0.39–1.75)	0.73 (0.26–2.01)	1.01, $P = 0.43$ (0.98–1.04)
i Sporadic unilateral	3.74 (0.91–15.4)	0.81 (0.45–1.47)	1.00	1.35 (0.75–2.42)	1.18 (0.61–2.27)	0.89 (0.32–2.46)	0.52 (0.14–1.96)	1.00, $P = 0.95$ (0.96–1.04)
ii Assumed old germ cell mutation	0.10 (0.00–2.61)	0.31 (0.08–1.15)	1.00	2.60 (0.70–9.60)	0.41 (0.06–2.90)	1.76 (0.14–22.1)	1.81 (0.05–65.4)	1.03, $P = 0.52$ (0.94–1.14)
iii Assumed new germ cell mutation	0.16 (0.02–1.68)	0.50 (0.22–1.16)	1.00	1.36 (0.60–3.06)	0.68 (0.21–2.20)	0.46 (0.09–2.21)	2.96 (0.21–41.7)	1.04, $P = 0.22$ (0.98–1.10)

[a] The models included the following confounder-variables: deprivation score and parity.

[b] 95% confidence interval.

[c] Reference category.

[d] Analysis in EGRET using individual years of age. The result is the odds ratio that occurs when the parental age changes by one year.

[e] There were no mothers aged 40+ years for this group.

extent. Thus we have chosen to present results for mother's age without simultaneous adjustment for father's, and vice versa.

Parity and maternal age are correlated, and there may also be an association between parity and deprivation. When changes from adding variables to different models were assessed, we found that while there was a strong effect of maternal age on ALL risk (Table 3), neither parity nor deprivation explained this. There was a highly significant effect of parity if maternal age was already in the model; moreover the effect of mother's age was stronger if parity was already in the model. Both these statements were true whether or not deprivation was allowed for. The deprivation effect was similar whether or not these other variables were included. From the results we conclude that parity and maternal age independently affect the child's ALL risk and that any effect of deprivation is not explained by the age or parity effects. Table 4 shows the ALL OR for parity (a) unadjusted, (b) adjusted for deprivation only, and (c) adjusted for deprivation and maternal age. Including deprivation in the model did not alter the parity OR, but the inclusion of maternal age did.

Discussion

We did not find statistically significant evidence to support hypothesis 1 for retinoblastoma. A non-significantly raised OR for assumed new germ cell mutations was found in relation to older mothers in addition to fathers. It was not possible to disentangle the age effects for each parent, because of the strong

Table 4 Odds ratios (OR) for childhood leukaemias by parity (conditional logistic regression)

Diagnostic group	Parity	No. of cases	No. of controls	Unadjusted OR (95% CI)	Adjusted OR I[a] (95% CI)	Adjusted OR II[b] (95% CI)
Acute lymphoblastic leukaemia	0[c]	1255	1199	1.00	1.00	1.00
	1	1029	1027	0.95 (0.85–1.08)	0.95 (0.84–1.07)	0.92 (0.82–1.04)
	2	404	419	0.92 (0.78–1.08)	0.92 (0.78–1.08)	0.84 (0.71–0.99)
	3	158	181	0.82 (0.65–1.04)	0.83 (0.65–1.05)	0.72 (0.56–0.93)
	4	53	57	0.89 (0.61–1.30)	0.89 (0.61–1.30)	0.72 (0.48–1.06)
	⩾5	43	59	0.69 (0.46–1.03)	0.70 (0.47–1.05)	0.52 (0.34–0.80)
	Effect of trend in parity[d]			0.95 (0.91–0.99)	0.95 (0.91–0.99)	0.90 (0.86–0.95)
	P for trend in parity			0.014	0.016	<0.001
Acute lymphoblastic leukaemia,	0[c]	890	818	1.00	1.00	1.00
ages 1–5 only	1	710	723	0.90 (0.78–1.03)	0.89 (0.77–1.03)	0.85 (0.73–0.98)
	2	258	278	0.84 (0.69–1.03)	0.84 (0.69–1.03)	0.74 (0.60–0.91)
	3	103	123	0.76 (0.57–1.01)	0.76 (0.57–1.01)	0.64 (0.47–0.87)
	4	30	34	0.81 (0.49–1.33)	0.80 (0.49–1.31)	0.61 (0.36–1.03)
	⩾5	27	42	0.59 (0.36–0.96)	0.58 (0.35–0.95)	0.43 (0.26–0.73)
	Effect of trend in parity[d]			0.92 (0.87–0.97)	0.92 (0.87–0.97)	0.86 (0.81–0.92)
	P for trend in parity			0.002	0.002	<0.001
Acute non-lymphoblastic leukaemia	0[c]	207	191	1.00	1.00	1.00
	1	172	205	0.75 (0.55–1.01)	0.75 (0.55–1.01)	0.77 (0.56–1.06)
	2	81	76	0.97 (0.67–1.42)	0.95 (0.65–1.40)	1.00 (0.66–1.49)
	3	39	26	1.36 (0.79–2.34)	1.30 (0.75–2.25)	1.35 (0.76–2.42)
	4	15	17	0.85 (0.40–1.80)	0.79 (0.37–1.69)	0.80 (0.35–1.84)
	⩾5	12	11	0.98 (0.41–2.35)	1.07 (0.44–2.61)	1.00 (0.39–2.58)
	Effect of trend in parity[d]			1.02 (0.93–1.12)	1.02 (0.92–1.12)	1.01 (0.90–1.13)
	P for trend in parity			0.66	0.72	0.84

[a] Adjusted for deprivation score.

[b] Adjusted for maternal age and deprivation score.

[c] Reference category.

[d] The result is the odds ratio that occurs when parity changes by one unit.

correlation between maternal and paternal ages. It would be very difficult or impossible to identify a big enough data set where parental ages were not closely correlated. Pertaining to hypothesis 2, there was an increasing risk of ALL with increasing maternal age, but this was not simply because of the association with Down syndrome. Hypothesis 3 was supported; there was an important protective effect of increasing parity on the risk of ALL. Concerning hypothesis 4, we confirmed that residence at birth in a community with greater deprivation did appear to be associated with a decreased risk of ALL, although the main adjusted result was not statistically significant. There was no significant effect on ALL risk of individual social class based on parental occupation, but the numbers were smaller in those analyses and there was a suggestion of an effect in the same direction as was found with the community-based measure of deprivation.

Critique of this study

A major strength of this study was its large size. Over 10 000 children with cancer were included, along with matched controls. The hypotheses were outlined before the analyses were planned. Although multiple comparisons were made in order to produce parental age data for different types of cancer, these were supplementary to the hypotheses. Information on the variables of interest was derived from the birth records of cases and controls, i.e. before the case group's cancers were diagnosed. There was no recall bias, and no problems due to differential participation of cases and controls. We therefore have a degree of confidence in the accuracy of the estimates that cannot be achieved with some other study designs. The variables available from birth records are probably not themselves aetiological factors. Instead, they are likely to be correlates of other factors that may be relevant (further discussed below). Another issue is possible overmatching in relation to socioeconomic factors (a result of matching on birth registration sub-district). This could make it more difficult to find real differences between cases and controls, but the effect of this may not have been very important because of the relatively large sizes of the areas used.

Comparisons with previous studies

In 1958, Stewart *et al.*[28] found an excess of firstborns among children who had died from leukaemia. They also found an increased risk of leukaemia death in relation to maternal age over 40 years (children with Down syndrome had been excluded).

Table 5 Odds ratios (OR) for childhood leukaemias by deprivation score and its components (conditional logistic regressions for all)

Diagnostic group	Variable	Categories	No. of cases	No. of controls	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Acute lymphoblastic leukaemia						
	Whole sample, 2942 pairs					
	Deprivation score	1st fifth (most affluent)[b]	459	428	1.00	1.00
		2nd fifth	462	428	0.99 (0.82–1.21)	1.01 (0.83–1.22)
		3rd fifth	508	506	0.92 (0.76–1.11)	0.94 (0.78–1.13)
		4th fifth	617	654	0.85 (0.70–1.02)	0.87 (0.72–1.06)
		5th fifth (most deprived)	896	926	0.85 (0.71–1.03)	0.91 (0.75–1.10)
		Effect of trend in score[c]			0.95 (0.91–1.00)	0.97 (0.93–1.01)
		P for trend in score			0.03	0.15
	Proportion in low social class	1st fifth (least in classes IV or V)[b]	511	451	1.00	1.00
		2nd fifth	536	546	0.85 (0.71–1.02)	0.85 (0.71–1.02)
		3rd fifth	579	548	0.91 (0.76–1.09)	0.92 (0.77–1.10)
		4th fifth	606	623	0.83 (0.69–0.99)	0.85 (0.71–1.02)
		5th fifth (most in classes IV or V)	710	774	0.76 (0.64–0.92)	0.80 (0.66–0.96)
		Effect of trend in score[c]			0.94 (0.91–0.98)	0.96 (0.92–1.00)
		P for trend in score			0.007	0.04
Acute non-lymphoblastic leukaemia						
	Whole sample, 526 pairs					
	Deprivation score	1st fifth (most affluent)[b]	85	85	1.00	1.00
		2nd fifth	67	92	0.74 (0.48–1.15)	0.74 (0.47–1.16)
		3rd fifth	90	63	1.54 (0.96–2.48)	1.54 (0.94–2.50)
		4th fifth	124	133	0.98 (0.64–1.51)	0.94 (0.61–1.47)
		5th fifth (most deprived)	160	153	1.13 (0.71–1.77)	1.07 (0.67–1.73)
		Effect of trend in score[c]			1.04 (0.94–1.16)	1.03 (0.93–1.15)
		P for trend in score			0.43	0.59
	Proportion in low social class	1st fifth (least in classes IV or V)[b]	86	98	1.00	1.00
		2nd fifth	91	90	1.17 (0.77–1.80)	1.14 (0.74–1.76)
		3rd fifth	102	107	1.13 (0.75–1.70)	1.06 (0.70–1.62)
		4th fifth	117	109	1.29 (0.84–1.96)	1.20 (0.78–1.85)
		5th fifth (most in classes IV or V)	130	122	1.31 (0.84–2.05)	1.25 (0.79–1.98)
		Effect of trend in score[c]			1.07 (0.96–1.18)	1.05 (0.95–1.17)
		P for trend in score			0.22	0.35

[a] The following confounder variables were included in the conditional logistic regression models: maternal age and parity.

[b] Reference category.

[c] The result is the odds ratio that occurs when the score category changes by one.

Studies by MacMahon and Newill[29] and Stark and Mantel[30] in the 1960s both recorded independent effects of maternal age and birth order on the risk of leukaemia death; these were in the same directions as those found for ALL in the current study. Buckley *et al*. showed an effect in the opposite direction, i.e. an increased risk of ALL in relation to higher birth order.[31] Other reasonably large studies found no significant association between childhood leukaemia or ALL and birth order or number of older siblings.[32–35] Our present case-control study is the largest on this topic that we know of. The clear finding of a protective effect on ALL risk of increasing parity, with a well-defined trend and selectivity for ALL (i.e. no association for ANLL) is extremely interesting. There is good statistical precision, and a relative absence of bias. This is arguably the most convincing evidence to date that higher parity is associated with a reduced risk of childhood ALL. This study gives some support to the finding of a previous British ecological study, which recorded a higher incidence of childhood lymphocytic leukaemia in relation to measures of higher socioeconomic status.[36] Similar findings would be expected, given the overlap of cases between the two studies, and the use of socioeconomic measures based on the same census data. One advantage of the present study is its case-control design. Further work is needed on the relationship between social class and ALL because of different findings in some countries, problems related to participation in studies that involve recruitment of families, and the need for studies with very large numbers and individually assigned measures of social class.

Table 6 Odds ratios (OR) for childhood leukaemias by social class (unmatched analyses)

Diagnostic group	Variable	Categories	No. of cases	No. of controls	Minimally adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Acute lymphoblastic leukaemia						
	Social class (individual)	I or II[c]	72	60	1.00	1.00
		IIIN or IIIM	103	109	0.80 (0.52–1.25)	0.81 (0.51–1.27)
		IV or V	44	46	0.79 (0.46–1.36)	0.86 (0.49–1.53)
		Effect of trend in category[d]			0.88 (0.68–1.15)	0.92 (0.69–1.22)
		P for trend			0.36	0.55
Acute non-lymphoblastic leukaemia						
	Social class (individual)	I or II[c]	10	5	1.00	1.00
		IIIN or IIIM	15	11	0.62 (0.14–2.65)	0.19 (0.02–1.58)
		IV or V	7	11	0.25 (0.05–1.20)	0.12 (0.02–0.82)
		Effect of trend in category[d]			0.49 (0.22–1.07)	0.39 (0.16–0.94)
		P for trend			0.08	0.04

[a] Adjusting only for birth registration year and sex.

[b] The following confounder variables were included in the models: birth registration year, sex, maternal age and parity.

[c] Reference category.

[d] The result is the odds ratio that occurs when the social class category changes by one.

Reasons for the parity association

The strong and statistically significant relationship between childhood ALL and parity is of particular interest. Much discussion about this has revolved around the possibility of associations with infections in early childhood,[8,9] as discussed earlier. Birth order is relevant to Greaves' hypothesis because first-born children may be more likely to have delayed exposure to early childhood infections, as compared with those who have older siblings that attend day care or school. Our parity findings could therefore give some indirect support to Greaves' hypothesis. On the other hand, findings from recent case-control studies that have tested Greaves' hypothesis more directly by considering infections in early childhood have been mixed. One study supported the hypothesis,[7] while others found little or no support.[15,34,35] The hypotheses about childhood leukaemia and the pattern of infections in early childhood, and about population mixing and specific infectious agents have yet to be confirmed. Further work that tests these hypotheses more directly is needed, and is being done in Britain and elsewhere. Infections and immunological isolation are not the only possible explanations for parity differences. Parents do many things differently for firstborns as compared with subsequent children, and several pregnancy and household exposures may be less likely for children with higher birth orders. For example, first-time mothers may be more likely to take certain specific medications in pregnancy.[30] Those planning aetiological investigations to explain the parity effect should therefore consider investigating several possible exposures that would be expected to vary with birth order.

Acknowledgements

We are grateful to Mr Charles Stiller and to all the other people who have worked on the NRCT over many years. We thank all those who have provided information to the registry, including the regional cancer registries, many doctors, the Office for National Statistics and members of the UK Children's Cancer Study Group. We thank Mrs Beverley Botting for facilitating the collaboration of the ONS, and Dr Joanne Dockerty for her helpful comments. Dr John Dockerty was supported by the Nuffield Dominions Trust. This work was undertaken by the Childhood Cancer Research Group which receives support from the Department of Health and the Scottish Ministers. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health and the Scottish Ministers.

KEY MESSAGES

- This was a large case-control study involving linkage of childhood cancer registrations to birth records.
- The risk of childhood acute lymphoblastic leukaemia (ALL) increased significantly with increasing parental ages.
- Independently of this, there was a clear relationship between higher parity and lower risk of childhood ALL.
- The effects of community-based deprivation score and individual social class on childhood ALL were not statistically significant.

References

[1] Office for National Statistics. *Social Trends 29, 1999 Edition*. London: The Stationery Office, 1999.

[2] Tarín JJ, Brines J, Cano A. Long-term effects of delayed parenthood. *Hum Reprod* 1998;**13:**2371–76.

[3] Breart G. Delayed childbearing. *Eur J Obstet Gynecol Reprod Biol* 1997; **75:**71–73.

[4] Shen JJ, Williams BJ, Zipursky A *et al*. Cytogenetic and molecular studies of Down syndrome individuals with leukemia. *Am J Hum Genet* 1995;**56:**915–25.

[5] Wilcox AJ, Sandler DP, Everson RB. Using father's age to explore the role of germ cell mutation as a cause of human cancer. *Int J Epidemiol* 1988;**17:**469–71.

[6] Chow W, Linet MS, Liff JM, Greenberg RS. Cancers in children. In: Schottenfeld D, Fraumeni JF Jr (eds). *Cancer Epidemiology and Prevention*. New York: Oxford University Press, 1996, pp.1331–69.

[7] McKinney PA, Juszczak E, Findlay E, Smith K, Thomson CS. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. *Br J Cancer* 1999;**80:**1844–51.

[8] Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia* 1988;**2:**120–25.

[9] Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet* 1988;**ii:**1323–27.

[10] Neglia JP, Severson RK, Linet MS. A reply to MF Greaves: toward a testable etiology of childhood acute lymphoblastic leukemia. *Leukemia* 1990;**4:**517–21.

[11] Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 1995;**71:**1–5.

[12] Draper GJ, Kroll ME, Stiller CA. Childhood cancer. *Cancer Surv* 1994; **19/20:**493–517.

[13] Greaves MF, Alexander FE. An infectious etiology for common acute lymphoblastic leukaemia in childhood? *Leukemia* 1993;**7:**349–60.

[14] Draper GJ, Elliott P. Variations in incidence rates and factors affecting them—summary. In: Draper G (ed.). *The Geographical Epidemiology of Childhood Leukaemia and Non-Hodgkin Lymphomas in Great Britain, 1966–83*. London: HMSO, 1991, pp.57–60.

[15] Dockerty JD, Skegg DCG, Elwood JM, Herbison GP, Becroft DMO, Lewis ME. Infections, vaccinations, and the risk of childhood leukaemia. *Br J Cancer* 1999;**80:**1483–89.

[16] McLoone P, Ellaway A. Postcodes don't indicate individuals' social class. *Br Med J* 1999;**319:**1003.

[17] Webster T. Can individual-level studies have ecologic bias? Poster presentation at the Conference on the Analysis and Interpretation of Disease Clusters and Ecological Studies 16th–17th December 1999. London: Royal Statistical Society. 1999.

[18] Quesnel S, Malkin D. Genetic predisposition to cancer and familial cancer syndromes. *Pediatr Oncol* 1997;**44:**791–808.

[19] Stiller CA, Allen MB, Eatock EM. Childhood cancer in Britain: the National Registry of Childhood Tumours and incidence rates 1978–1987. *Eur J Cancer* 1995;**31A:**2028–34.

[20] Stiller CA, O'Connor CM, Vincent TJ, Draper GJ. The national registry of childhood tumours and the leukaemia/lymphoma data for 1966–83. In: Draper G (ed.). *The Geographical Epidemiology of Childhood Leukaemia and Non-Hodgkin Lymphomas in Great Britain, 1966–83*. London: HMSO, 1991, pp.7–16.

[21] Kramárová E, Stiller CA, Ferlay J *et al*. *International Classification of Childhood Cancer 1996.* IARC Technical Report No. 29. Lyon: International Agency for Research on Cancer, 1996.

[22] Draper GJ, Little MP, Sorahan T *et al*. *Cancer in the Offspring of Radiation Workers—A Record Linkage Study.* Didcot, Oxon: National Radiological Protection Board, 1997, pp.1–72.

[23] Office of Population Censuses and Surveys. *Mortality Statistics, Perinatal and Infant: Social and Biological Factors. Review of the Registrar General on Deaths in England and Wales, 1986*. Series DH3 no. 20. London: Her Majesty's Stationery Office, 1988, pp.1–72.

[24] Office of Population Censuses and Surveys. *Standard Occupational Classification. Vol. 3: Social Classifications and Coding Methodology*. London: HMSO, 1991.

[25] Carstairs V, Morris R. *Deprivation and Health in Scotland*. Aberdeen: Aberdeen University Press, 1991, pp.1–334.

[26] Office of Population Censuses and Surveys. *Birth Statistics. Historical Series of Statistics from Registrations of Births in England and Wales, 1837–1983*. Series FM1 no. 13. London: Her Majesty's Stationery Office, 1987.

[27] Statistics and Epidemiology Research Corporation and Cytel Software Corporation. *EGRET Reference Manual, Rev. 3*. Seattle: Statistics and Epidemiology Research Corporation and Cytel Software Corporation, 1993.

[28] Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. *Br Med J* 1958;**i:**1495–508.

[29] MacMahon B, Newill VA. Birth characteristics of children dying of malignant neoplasms. *J Natl Cancer Inst* 1962;**28:**231–44.

[30] Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. *J Natl Cancer Inst* 1966;**37:**687–98.

[31] Buckley JD, Buckley CM, Ruccione K *et al*. Epidemiological characteristics of childhood acute lymphocytic leukaemia. Analysis by immunophenotype. *Leukemia* 1994;**8:**856–64.

[32] Fasal E, Jackson EW, Klauber MR. Birth characteristics and leukemia in childhood. *J Natl Cancer Inst* 1971;**47:**501–09.

[33] Westergaard T, Andersen PK, Pedersen JB *et al*. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. *J Natl Cancer Inst* 1997;**89:**939–47.

[34] Schüz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. *Br J Cancer* 1999;**80:**585–90.

[35] Neglia JP, Linet MS, Shu XO *et al*. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. *Br J Cancer* 2000;**82:**234–40.

[36] Draper GJ, Vincent TJ, O'Connor CM, Stiller CA. Socio-economic factors and variations in incidence rates between county districts. In: Draper G (ed.). *The Geographical Epidemiology of Childhood Leukaemia and Non-Hodgkin Lymphomas in Great Britain, 1966–83*. London: HMSO, 1991, pp.37–45.