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Bayesian methods for early detection of changes in childhood cancer incidence: Trends for acute lymphoblastic leukaemia are consistent with an infectious aetiology

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ABSTRACT

Published data on time trends in the incidence of childhood leukaemia show inconsistent patterns, with some studies showing increases and others showing relatively stable incidence rates. Data on time trends in childhood cancer incidence from the Childhood Cancer Registry of Piedmont, Italy were analysed using two different approaches: standard Poisson regression and a Bayesian regression approach including an autoregressive component. Our focus was on acute lymphoblastic leukaemia (ALL), since this is hypothesised to have an infectious aetiology, but for purposes of comparison we also conducted similar analyses for selected other childhood cancer sites (acute non-lymphoblastic leukaemia (AnLL), central nervous system (CNS) tumours and neuroblastoma (NB)). The two models fitted the data equally well, but led to different interpretations of the time trends. The first produced ever-increasing rates, while the latter produced non-monotonic patterns, particularly for ALL, which showed evidence of a cyclical pattern. The Bayesian analysis produced findings that are consistent with the hypothesis of an infectious aetiology for ALL, but not for AnLL or for solid tumours (CNS and NB). Although sudden changes in time trends should be interpreted with caution, the results of the Bayesian approach are consistent with current knowledge of the natural history of childhood ALL, including a short latency time and the postulated infectious aetiology of the disease.

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1. Introduction

Temporal variations in the incidence of childhood leukaemia have been the focus of several studies in the past decade. Overall, the published data show increasing trends, although there is wide variation both in the estimates provided and in the methods of data analysis. Table 1 summarises the findings of recent studies conducted in Western

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Table 1 – Childhood leukaemia and acute lymphoblastic leukaemia incidence trends in scientific reports published in 1966–2005 (periods of observation: 1953–2001)

Reference	Area	Period	Age (years)	Leukaemia[a]	No. of cases per year	Acute lymphoblastic leukaemia[a]	No. of cases per year
Bunin et al. [1]	USA (not SEER) Delaware	1970–1989	0–14	↔	70	↔	54
Gurney et al. [2]	USA (SEER)	1974–1991	0–14	↑	210	↑	155
Linet et al. [3]	USA (SEER)	1975–1995	0–14	↔	209		
Liberson et al. [4]	USA (SEER)	1973–1995	0–14			↔	159
McNeil et al. [5]	USA (SEER)	1973–1998	0–19			↑	178
Xie et al. [6]	USA (SEER)	1973–1998	0–19	↑	255	↑	186
Ries et al. [7]	USA (SEER)	1975–2001	0–14	↑ Since 1987: ↔	255	↑ Since 1987: ↔	186
Dockerty et al. [8]	New Zealand	1953–1990	0–14	↑	35	↑ 1968–1990	28
McWhirter et al. [9]	Queensland, Australia	1973–1988	0–12			↔	19
McWhirter et al. [10]	Australia	1982–1991	0–14	↑ AnLL	175	↔	138
Draper et al. [11]	UK	1953–1991	0–14	↑	430	↑	343
Blair and Birch [12]	Manchester, UK	1954–1988	0–14			↑	25
McNally et al. [13]	Manchester, UK	1954–1998	0–14			↑	25
McNally et al. [14]	Manchester, UK	1980–1998	1–4			↑ Pre B-cell subtype	10
Cotterill et al. [15]	North of England, UK	1968–1995	0–14	↑ Haematological malignancies	24		20
Feltbower et al. [16]	Yorkshire, UK	1974–1997	1–4			↑	11
Swerdlow et al. [17]	Scotland	1960–1990	0–14	↑	27		
Coebergh et al. [18]	Netherlands	1973–1986	0–14	↔	112	↔	90
Reedijk et al. [19]	Southern Netherlands	1973–1999	0–14	↔	10	↔	8
Hjalgrim et al. [20]	Nordic countries NSPHO	1982–2001	0–14	↔	221 (approx.)	↔	173
Dreifaldt et al. [21]	Sweden	1960–1998	0–14	↑	71	↑ Since 1978: ↔	43
Desandes et al. [22]	France	1990–1999	0–14	↔	128	↔	100
Gonzalez et al. [23]	Tarragona, Spain	1980–1997	0–14	↔	6		
Magnani et al. [24]	Piedmont, Italy	1975–1998	0–14	↑	33	↑	26

The age range considered is 0–14 years unless explicitly stated.
a ↑ (↔) indicates evidence of positive (no) trend.

countries with periods of observation ranging from 1953 to 2001.

The overall pattern from these studies is that the incidence of all leukaemias, and especially acute lymphoblastic leukaemia (ALL), has been either increasing or stable over the last few decades. Thus, there are differences in the time trends between and sometimes within geographical areas. This is apparent for the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) studies, which include overlapping databases analysed using different statistical methods and epidemiological criteria, yielding different conclusions. The most evident increases are in children aged about 3 years, the age at which ALL incidence peaks, and in the precursor B-cell ALL subtype. It is also noteworthy that the increases in incidence were greatest in the earlier years of observation, while incidence has been more stable since the 1980s [7,20,21] (Table 1).

Changes in disease incidence over time are usually attributed primarily to changes in risk factors, although they may also be influenced by changes in diagnostic or classification procedures, differences in levels of ascertainment, or chance. Since little is known regarding the aetiology of childhood leukaemia, it is important to interpret correctly variations in incidence over time in order to determine whether such variations are due to changes in diagnostic or classification procedures, or whether they are related to putative causal factors. However, different risk factors may produce different time trends. In particular, cancers that (primarily) have an infectious aetiology may show cyclical effects, whereas cancers that (primarily) have a non-infectious aetiology are more likely to show gradual monotonic increases (or decreases) over time.

In this study we analysed data on the incidence of childhood cancer in Piedmont, Italy during 1975–2001. Our focus was on ALL, since this is hypothesised to have an infectious aetiology [25–27], but for purposes of comparison we also conducted similar analyses for selected other childhood cancer sites (acute non-lymphoblastic leukaemia (AnLL), central nervous system (CNS) tumours and neuroblastoma (NB)) which were not considered to have a primarily infectious aetiology (although there is, in fact, some preliminary evidence that exposure to infections before birth, or at the time of birth, may be associated with the risk of brain tumours in children [28–30]).

The standard method for analysing such time trend data is to estimate the annual percentage change (APC) using Poisson regression with age group and calendar year as covariates. Such a model, including only linear terms, assumes that changes in incidence rates follow a monotonic increase or decrease, and hence it is not suitable to detect changes in the direction of the incidence time trend. It is possible to fit Poisson models with both linear and quadratic terms, and

appropriately modified versions of age-period-cohort models have been proposed as early as 1993 [31,32], but they have not become usual practice in time trend analysis. We therefore also tested a Bayesian approach. Models of this type include random terms in the linear predictor and allow accommodation of overdispersion (which is frequently observed in practice). The attractiveness of these models is their lack of restrictive assumptions about functional dependency on time, as well as their flexibility for full assessment of the uncertainty in the estimated random effects and functions of model parameters [33].

2. Materials and methods

We analysed data for new ALL cases ($n = 688$) in children in Piedmont, by age (0, 1–4, 5–9 and 10–14 years) and year of diagnosis (from 1975 to 2001), as recorded by the Childhood Cancer Registry of Piedmont (CCRP). This is a population-based registry which, since 1967, has recorded incident cases of cancer in children (aged less than 15 years) resident in the region. The procedures and criteria for inclusion in the CCRP database, follow-up and coding of cancer types have been reported elsewhere [24,34]. The present analyses are limited to the period 1975–2001 in order to exclude the effect of improvement in diagnostic methods of the early 1970s [24], before which the proportion of microscopically confirmed diagnoses was too low to allow separate analyses for different types of leukaemia. The quality of ascertainment of ALL cases has been satisfactory [24,34] and constant over the period covered by our investigation.

For comparison purposes, we have also analysed the incidence temporal behaviour of AnLL ($n = 145$) from 1975 to 2001, and of CNS tumours ($n = 753$) and NB ($n = 254$) from 1967 to 2001.

Incidence rates were calculated per million children per year and refer to the population resident in Piedmont in the same period.

In addition to the standard Poisson regression model, a Bayesian non-parametric Generalised Linear Mixed Model (GLMM) with a second-order autoregressive error component was also used. The model was implemented with WinBugs [35], and the model specification is given in the Appendix. Goodness-of-fit was assessed through the Akaike Information Criterion [36] (AIC) for the Poisson model and through the Deviance Information Criterion [37] (DIC) for both Poisson and Bayesian autoregressive (BAR) models.

3. Results

Fig. 1 shows the observed and predicted age-adjusted ALL incidence rates by calendar year of diagnosis for the period 1975–2001 (upper curves). Both the Poisson regression and BAR models fitted the data equally well, with a slightly smaller error for the BAR model (Poisson: AIC = 430 (4 df), DIC = 434 (7 df); BAR: DIC = 457 (20 df). Sum of squared Pearson residuals: Poisson: 1041, BAR: 822).

The predictions do not differ greatly for most of the individual years considered, but the overall shape of the models is different. In particular, the BAR expected rates do not exhibit a monotonically increasing pattern: in the first half of the study period they oscillate around an average value of 35 cases/10^6 years, then show a sharp increase in the years from 1989 until 1997, and finally begin to decline from 1998.

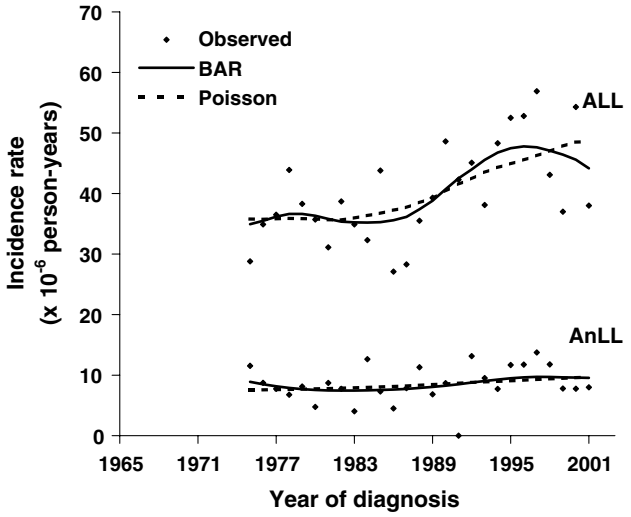

Fig. 1 – Childhood Cancer Registry of Piedmont. Observed (dots) and predicted age-adjusted acute lymphoblastic leukaemia (ALL, upper curves) and acute non-lymphoblastic leukaemia (AnLL, lower curves) incidence rates versus calendar year of diagnosis for children (0–14 years of age) in 1975–2001. Predictions by the Bayesian autoregressive model (BAR, thick straight line) and the Poisson model (dashed line).

Fig. 1 also shows the corresponding analyses for AnLL (lower curves). For this cancer type, the Poisson and BAR models produced similar patterns (Poisson: AIC = 316 (4 df), DIC = 317 (6 df) ; BAR: DIC = 331 (13 df)).

For purposes of comparison, Fig. 2 shows the observed and predicted age-adjusted CNS tumours and NB incidence rates for the period 1967–2001. The Poisson regression and BAR models yielded very similar patterns with similar goodness-of-fit (CNS tumours: Poisson: AIC = 567 (4 df), DIC = 573 (8 df); BAR: DIC = 596 (20 df); NB: Poisson: AIC = 416 (4 df), DIC = 418 (6 df); BAR: DIC = 442 (19 df)).

4. Discussion

In this study CCRP data on the incidence of ALL, and other selected childhood cancer sites were analysed using a Bayesian approach in order to assess the possibility of a deviation from the monotonic increasing trend predicted by standard regression methods. Both the Poisson and BAR regressions produced models showing increases in incidence for ALL. However, while the former produced a model involving monotonic increases over time, the latter model showed broad oscillations. On the other hand, the two approaches produced very similar patterns for AnLL, CNS tumours and NB.

The choice between statistical models is usually carried out through a posteriori criteria, such as goodness-of-fit sta-

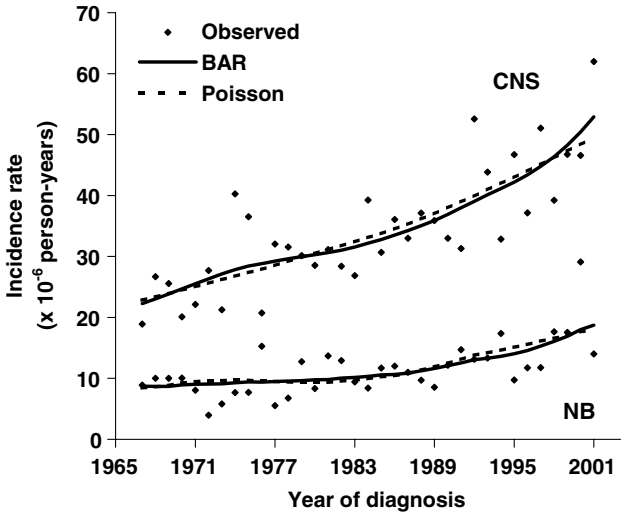

Fig. 2 – Childhood Cancer Registry of Piedmont. Observed (dots) and predicted age-adjusted central nervous system tumour (CNS, upper curves) and neuroblastoma (NB, lower curves) incidence rates versus calendar year of diagnosis for children (0–14 years of age) in 1967–2001. Predictions by the Bayesian autoregressive model (BAR, thick straight line) and the Poisson model (dashed line).

tistics and residual analysis, and sometimes also a priori considerations about the plausibility of model assumptions. This paper shows an example of a situation where both the standard Poisson and the BAR model fit the same data equally well (thus providing no useful statistical criteria for the choice of model) and yet lead to different interpretations of the shape of the time trends for ALL. Poisson regression fixes the overall shape of the curve and thereby gives more weight to long-term trends, while BAR is more flexible and more responsive to short-term changes. Flexible methods (i.e., compatible with non-linear behaviour) are thus capable of providing an 'early warning' of changes in the direction of the incidence trend and are more efficient in identifying structures in the data than the standard Poisson model, forced within the limit of a linear hypothesis on the effect estimates. On the other hand, a potential drawback of this and similar methods is that their estimates are very sensitive to short-term fluctuations, and may therefore be more susceptible to random variation. The choice of model therefore, in part, depends on the prior hypothesis (e.g., as to whether the cancer type has a predominantly infectious aetiology), although if there is sufficient data (and hence little random variation), then the Bayesian approach can be used routinely, and can identify conditions that have, or do not have, cyclical patterns (as in the examples presented here).

Bearing these considerations and limitations in mind, the findings presented here are of interest since they are consistent with the hypothesis of an infectious aetiology for ALL [25–27], given that infections commonly exhibit cyclical behaviour in time, and the short latency time for childhood cancer means that cancers with an infectious aetiology may also be expected to show cyclical time trends. AnLL (Fig. 1), CNS tumours and NB (Fig. 2), which are all considered to have a non-infectious aetiology, do not show similar oscillations. Although a possible involvement of infections in the aetiology of CNS and NB has been hypothesised [28–30], the evidence to date is not conclusive, and our findings do not support this suggestion. In fact, we have found that CNS and NB incidence has been monotonically increasing with time. Should an infectious aetiology be involved, the apparent lack of cyclical behaviour could be due to a weaker effect on these tumours than on ALL, or due to different infections (which did not experience epidemics during the period under study) being involved.

In summary, although sudden changes in time trends should be interpreted with caution, the results of the Bayesian approach are consistent with current knowledge of the natural history of childhood ALL, including a short latency time and the postulated infectious aetiology of the disease. Flexible methods such as the BAR approach proposed here are capable of detecting cyclical time trends patterns, and also of providing an 'early warning' of changes in the direction of cancer incidence trends.

Conflict of interest statement

None declared.

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Appendix

The logarithm of the mean number of cases in the jth age group and kth calendar year of diagnosis is assumed to satisfy

$$\log(\mu_{jk}) = \log n_{jk} + \alpha_j + \beta_k + \sigma u_k,$$

where n_{jk} denotes the person-years denominator and α_j denotes the fixed effect of age. The fixed effect trend β and the random effect vectors $\mathbf{u}$ model two different aspects of the variation of rates with calendar year. In particular, the model for $\mathbf{u}$ represents smooth variation over time, and is specified in the forward direction as a Gaussian second-order autoregressive model (each point is predicted by linear extrapolation from its two immediate predecessors rather than from just the latest one) (see Table A).

Table A – Childhood Cancer Registry of Piedmont: Parameter estimates for the fixed effects of the Poisson model estimated with Stata and Winbugs, and of the BAR model estimated with Winbugs, for acute lymphoblastic leukaemia (ALL), acute non-lymphoblastic leukaemia (AnLL), central nervous system (CNS) tumours and neuroblastoma (NB) in children (0–14 years of age)

Fixed effects (95%CI)	Model		Age 1–4[a] years	Age 5–9[a] years	Age 10–14[a] years	Year
ALL (1975–2001)	Poisson	Stata	1.685 (1.168; 2.202)	0.862 (0.338; 1.386)	0.225 (−0.311; 0.761)	0.012 (0.003; 0.022)
	Poisson	Winbugs	1.715 (1.229; 2.285)	0.891 (0.397; 1.469)	0.253 (−0.253; 0.842)	0.012 (0.003; 0.022)
	BAR	Winbugs	1.714 (1.207; 2.301)	0.892 (0.378; 1.486)	0.254 (−0.277; 0.858)	0.044 (−0.102; 0.128)
AnLL (1975–2001)	Poisson	Stata	−0.511 (−1.109; 0.087)	−0.649 (−1.233; −0.066)	−0.769 (−1.352; −0.186)	0.009 (−0.012; 0.030)
	Poisson	Winbugs	−0.493 (−0.072; 0.128)	−0.628 (−1.193; −0.024)	−0.749 (−1.311; −0.141)	0.009 (−0.012; 0.030)
	BAR	Winbugs	−0.485 (−1.069; 0.137)	−0.618 (−1.188; −0.009)	−0.735 (−1.308; −0.127)	0.1708 (0.002; 0.346)
CNS (1967–2001)	Poisson	Stata	0.507 (0.117; 0.896)	0.585 (0.203; 0.966)	0.248 (−0.138; 0.635)	0.023 (0.016; 0.030)
	Poisson	Winbugs	0.529 (0.151; 0.941)	0.607 (0.236; 1.015)	0.271 (−0.105; 0.682)	0.023 (0.016; 0.030)
	BAR	Winbugs	0.523 (0.149; 0.933)	0.604 (0.237; 1.006)	0.269 (−0.102; 0.675)	0.009 (−0.048; 0.056)
NB (1967–2001)	Poisson	Stata	−0.940 (−1.225; −0.654)	−2.455 (−2.848; −2.062)	−3.311 (−3.837; −2.785)	0.023 (0.010; 0.035)
	Poisson	Winbugs	−0.937 (−1.222; −0.647)	−2.462 (−2.866; −2.074)	−3.335 (−3.891; −2.822)	0.023 (0.011; 0.035)
	BAR	Winbugs	−0.934 (−1.22; −0.649)	−2.464 (−2.865; −2.075)	−3.336 (−3.892; −2.828)	−0.114 (−0.234; −0.014)

a Reference: age 0.

REFERENCES

1. Bunin GR, Feuer EJ, Witman PA, et al. Increasing incidence of childhood cancer: report of 20 years experience from the greater Delaware Valley Pediatric Tumor Registry. *Paediatr Perinat Epidemiol* 1996;**10**:319–38.
2. Gurney JG, Davis S, Severson RK, et al. Trends in cancer incidence among children in the US. *Cancer* 1996;**78**:532–41.
3. Linet MS, Ries LA, Smith MA, et al. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst* 1999;**91**:1051–8.
4. Liberson GL, Golden RJ, Blot WJ, et al. An examination of the sensitivity of reported trends in childhood leukaemia incidence rates to geographic location and diagnostic coding (United States). *Cancer Causes Control* 2000;**11**:413–7.
5. McNeil DE, Cote TR, Clegg L, et al. SEER update of incidence and trends in pediatric malignancies: acute lymphoblastic leukemia. *Med Pediatr Oncol* 2002;**39**:554–7. Discussion 552–553.
6. Xie Y, Davies SM, Xiang Y, et al. Trends in leukemia incidence and survival in the United States (1973–1998). *Cancer* 2003;**97**:2229–35. Erratum in: Cancer 2003, **98**, 659.
7. Ries LAG, Eisner MP, Kosary CL, et al., editors. *SEER Cancer Statistics Review, 1975–2001*. Bethesda, MD: National Cancer Institute; 2004. Available from: http://seer.cancer.gov/csr/1975_2001/.
8. Dockerty JD, Cox B, Cockburn MG. Childhood leukaemias in New Zealand: time trends and ethnic differences. *Br J Cancer* 1996;**73**:1141–7.
9. McWhirter WR, Petroeschevsky AL. Incidence trends in childhood cancer in Queensland, 1973–1988. *Med J Aust* 1991;**154**:453–5.
10. McWhirter WR, Dobson C, Ring I. Childhood cancer incidence in Australia, 1982–1991. *Int J Cancer* 1996;**65**:34–8.
11. Draper GJ, Kroll ME, Stiller CA. Childhood cancer. *Cancer Surv* 1994;**19–20**:493–517.
12. Blair V, Birch JM. Patterns and temporal trends in the incidence of malignant disease in children: I. Leukaemia and lymphoma. *Eur J Cancer* 1994;**30A**:1490–8.
13. McNally RJ, Cairns DP, Eden OB, et al. Examination of temporal trends in the incidence of childhood leukaemias and lymphomas provides aetiological clues. *Leukemia* 2001;**15**:1612–8.
14. McNally RJ, Birch JM, Taylor GM, et al. Incidence of childhood precursor B-cell acute lymphoblastic leukaemia in north-west England. *Lancet* 2000;**356**:485–6.
15. Cotterill SJ, Parker L, Malcolm AJ, et al. Incidence and survival for cancer in children and young adults in the North of England, 1968–1995: a report from the Northern Region Young Persons' Malignant Disease Registry. *Br J Cancer* 2000;**83**:397–403.
16. Feltbower RG, Moorman AV, Dovey G, et al. Incidence of childhood acute lymphoblastic leukaemia in Yorkshire, UK. *Lancet* 2001;**358**:385–7.
17. Swerdlow AJ, dos Santos Silva I, Reid A, et al. Trends in cancer incidence and mortality in Scotland: description and possible explanations. *Br J Cancer* 1998;**77**(Suppl. 3):1–54.
18. Coebergh JW, van der Does-van den Berg A, van Wering ER, et al. Childhood leukaemia in The Netherlands, 1973–1986: temporary variation of the incidence of acute lymphocytic leukaemia in young children. *Br J Cancer* 1989;**59**:100–5.
19. Reedijk AMJ, Janssen-Heijnen MLG, Louwman MWJ, et al. Increasing incidence and improved survival of cancer in children and young adults in Southern Netherlands 1973–1999. *Eur J Cancer* 2005;**41**:760–9.
20. Hjalgrim LL, Rostgaard K, Schmiegelow K, et al. Age- and sex-specific incidence of childhood leukemia by immunophenotype in the Nordic countries. *J Natl Cancer Inst* 2003;**95**:1539–44.
21. Dreifaldt AC, Carlberg M, Hardell L. Increasing incidence rates of childhood malignant diseases in Sweden during the period 1960–1998. *Eur J Cancer* 2004;**40**:1351–60.
22. Desandes E, Clavel J, Berger C, et al. Cancer incidence among children in France, 1990–1999. *Pediatr Blood Cancer* 2004;**43**:749–57.
23. Gonzalez JR, Fernandez E, de Toledo JS, et al. Trends in childhood cancer incidence and mortality in Catalonia, Spain, 1975–1998. *Eur J Cancer Prev* 2004;**13**:47–51.
24. Magnani C, Dalmasso P, Pastore G, et al. Increasing incidence of childhood leukemia in Northwest Italy, 1975–98. *Int J Cancer* 2003;**105**:552–7.

25. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with a nuclear reprocessing site in Britain. *Lancet* 1988;**2**:1323–7.
26. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia* 1988;**2**:120–5.
27. Alexander FE, Boyle P, Carli PM, et al. Spatial temporal patterns in childhood leukaemia: further evidence for an infectious origin. EUROCLUS project. *Br J Cancer* 1998;**77**:812–7.
28. Fear NT, Roman E, Ansell P, et al. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control* 2001;**12**:443–9.
29. McNally RJ, Cairns DP, Eden OB, et al. An infectious aetiology for childhood brain tumours? Evidence from space-time clustering and seasonality analyses. *Br J Cancer* 2002;**86**:1070–7.
30. Nyari TA, Dickinson HO, Hammal DM, et al. Childhood solid tumours in relation to population mixing around the time of birth. *Br J Cancer* 2003;**88**:1370–4.
31. Engeland A, Haldorsen T, Tretli S, et al. Prediction of cancer incidence in the Nordic countries up to the years 2000 and 2010. A collaborative study of the five Nordic Cancer Registries. *APMIS Suppl* 1993;**38**:1–124.
32. Moller B, Fekjaer H, Hakulinen T, et al. Prediction of cancer incidence in the Nordic countries up to the year 2020. *Eur J Cancer Prev* 2002;**11**(Suppl. 1):S1–S96.
33. Breslow NE, Clayton DG. Approximate inference in Generalized Linear Mixed Models. *J Am Stat Assoc* 1993;**88**:9–25.
34. Viscomi S, Pastore G, Mosso ML, et al. Population-based survival after childhood cancer diagnosed during 1970–98: a report from the Childhood Cancer Registry of Piedmont, Italy. *Haematologica* 2003;**88**:974–82.
35. Spiegelhalter DJ, Thomas A, Best NG. *WinBUGS Version 1.2 User Manual*. Cambridge, UK: MRC Biostatistics Unit; 1999.
36. Akaike H. A new look at statistical model identification. *IEEE Trans Automatic Control* 1974;**19**:716–22.
37. Spiegelhalter DJ, Best NG, Carlin BP, et al. Bayesian measures of model complexity and fit (with discussion). *J Roy Stat Soc B* 2002;**64**:583–639.