ORIGINAL ARTICLES

Survival after acute lymphocytic leukaemia: effects of socioeconomic status and geographic region

Julia A Schillinger, Pascale C Grosclaude, Satoshi Honjo, Michael J Quinn, Andy Sloggett, Michel P Coleman

Abstract

National cancer registry data, linked to an areal measure of material deprivation, were used to explore possible socioeconomic and regional variation in the survival of children (0–14 years) diagnosed with acute lymphocytic leukaemia (ALL) in England and Wales from 1971 to 1990. Survival analysis and Poisson regression were used to estimate observed (crude) survival probabilities and the adjusted hazard of death. There was little evidence of a socioeconomic gradient in survival. Regional differences in survival were observed over time. These differences were most pronounced in the first six months after diagnosis, and may be attributable to differential access to centralised paediatric oncology services or treatment protocols, or to the artefact of variations in regional cancer registry practice. Similar analyses should be repeated for other, less treatable childhood cancers. The results of this study can be used to help identify ways of reducing regional variation in survival.

(*Arch Dis Child* 1999;**80**:311–317)

Keywords: acute lymphocytic leukaemia; survival; socioeconomic status; regional variation; England and Wales

The Division of Sexually Transmitted Diseases Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Mailstop E-02, Atlanta, GA, 30333, USA
J A Schillinger

Cancer and Public Health Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
M P Coleman

Centre for Population Studies, London School of Hygiene and Tropical Medicine
A Sloggett

Tarn Cancer Registry, Chemin des Trois Tarn, 81000 Albi, France
P C Grosclaude

National Defense Medical College, 3–2 Namiki, Tokorozawa, Saitama 359–8513, Japan
S Honjo

Office for National Statistics, 1 Drummond Gate, London SW1V 2QQ, UK
M J Quinn

Correspondence to:
Dr Schillinger.

Accepted 10 November 1998

Socioeconomic inequalities in cancer survival have been described for adult cancers in the UK and elsewhere, with affluent patients having better survival than deprived patients for most cancers.[1–5] Geographic variations in cancer survival within and between countries have also been reported,[6–8] even after systematic attempts to eliminate potentially confounding differences in disease definitions, cancer registry practice, and analytic techniques.[9] Few studies have examined the influence of socioeconomic or geographical factors on survival after childhood cancers, although there is some evidence to suggest that socioeconomic differences may exist.[10–13]

The purpose of our study was to examine the independent effects of socioeconomic status and geographic region within England and Wales on the probability of survival for children diagnosed with acute lymphocytic leukaemia (ALL) during the period 1971–90. The UK government is working to develop an optimal strategy to ensure that effective treatment is available to all patients with cancer.[14] Advances in treatment over the past several decades have greatly improved the prospects for survival from leukaemia and other childhood cancers; in the UK there is evidence that the use of specialist paediatric oncology centres has contributed to this improved survival.[15–18] Demonstration of regional or socioeconomic differences in survival after a treatable malignancy such as ALL could suggest variations in the availability or use of treatment services for children, and could be used to inform strategies for improving the equity of health care provision, and measuring the success of such interventions.

Methods

DATA

All cases of ALL diagnosed from 1971 to 1990 in children aged 0–14 years in England and Wales were eligible for analysis. Data were routinely submitted to the Office for National Statistics (ONS) at intervals throughout that period by the 12 regional cancer registries as part of the national cancer registration scheme for England and Wales.[19] Since 1971, registered cancer patients have been flagged in the National Health Service Central Register, a virtually complete national person index. Under this system, the national cancer register is routinely notified of the death or emigration of any patient with cancer; patients with cancer are assumed to be alive unless death details have been recorded.

Information available for each patient included sex, date of birth, date of diagnosis, morphological code, vital status (with date of death recorded if death had occurred), postcode of residence at diagnosis, and cancer registry where the case was recorded. The Manual of Tumour Nomenclature and Coding (MOTNAC)[20] and the International Classification of Diseases for Oncology (ICD-O)[21] were used to assign a morphological code for each case (MOTNAC, cases diagnosed 1971–78; ICD-O, cases diagnosed 1979–90). Cases were assigned to diagnostic groups according to Birch and Marsden's classification scheme for childhood neoplasms[22] and ALL (subcategory I(a)), and other lymphoid leukaemia

(I(b)) were selected for analysis. A total of 602 patients were excluded from the analysis. These included 144 patients (2% of those eligible) for whom the recorded date of diagnosis was the same as the date of death. These patients were considered to have been documented by death certificate only and were excluded from the analysis because a survival time could not be calculated for them. An additional 458 cases (7%) were also excluded because they lacked other data necessary to calculate survival time, were missing other essential data, or were duplicate records. In the end, 5566 (90%) of 6168 eligible cases remained for analysis. Excluded cases were most likely to reside in the North Thames National Health Service (NHS) region (one of nine health service territories covering England and Wales), or to lack a postcode at diagnosis, but were otherwise similar to cases included in the analysis (data not shown).

The Carstairs index was used as a measure of material deprivation.[23] The Carstairs index is an areal measure of deprivation estimated at the level of the census enumeration district (ED), each of which includes about 500 people. In each ED, the values for four variables measured in the national census (percentage car ownership, household overcrowding, low social class of head of household* and male unemployment† are standardised to the mean value for all EDs in the UK, and summed to provide a Carstairs score. Five deprivation categories were defined by quintiles of the ranked distribution of Carstairs scores for all EDs in the UK, from the least deprived (or most affluent) 20% of the distribution to the most deprived 20%.‡ Each patient was assigned to a deprivation category by his or her ED, defined by the postcode of residence at diagnosis. Data from the 1981 census were used to assign the deprivation category for patients diagnosed between 1971 and 1985; for patients diagnosed between 1986 and 90, the 1991 census data were used.

For each patient resident in England, their NHS region, as defined at 1 April 1997, was determined by their postcode at the time of diagnosis. Patients with a postcode from Wales were assigned to that region.

ANALYSIS

Survival time for each case was calculated as the number of days between diagnosis and death, and converted to elapsed years by dividing by 365.25. Patients were censored from the analysis at emigration, or 31 December 1995 (whichever occurred first). Crude survival probability was estimated with the methods described by Kaplan and Meier,[24] using STATA software,[25] and examined for study subgroups defined by sex, age at diagnosis, five-year calendar period of diagnosis, deprivation category, and NHS region of residence at diagnosis.§ Age at diagnosis was treated as a discrete variable, using categories shown previously to have prognostic importance: under 2, 2–9, and 10–14 years.[17] The log rank statistic[26] was used to test the significance of differences between study subgroups in overall survival, as well as between estimates of survival at one, five, and 10 years.

Time trends in survival within regions were estimated by linear regression as the percentage change for each five-year period in the mean probability of survival for patients diagnosed in consecutive calendar periods (1971–75, 1976–80, 1981–85, and 1986–90).

To examine the independent effects of material deprivation and socioeconomic status, we used Poisson regression to model the hazard of death associated with deprivation category and with NHS region in the five years after diagnosis, while adjusting for calendar period of diagnosis, sex, and single year of age at diagnosis. Only those patients to whom a deprivation category could be assigned were included in the hazard analyses. Hazards were expressed as ratios to describe the relative hazards associated with particular deprivation categories, or residence in a particular NHS region. The most affluent group was used as the reference category for estimates of the hazard of death associated with deprivation, and the Anglia and Oxford NHS region was used as the reference group for estimates of secular trend in the hazard of death within and between regions. The Anglia and Oxford NHS region was selected as the referent group because the numbers of cases occurring in that region were large enough to permit stable estimates of survival, and case ascertainment and follow up are known to be of high quality in that region.[27 28] Proportional hazards were assumed.

Socioeconomic and region specific factors could differentially affect short term (compared with longer term) survival after diagnosis with ALL and this might not be evident in the overall five year hazard of death. For this reason, we compared the hazard of death during two successive time intervals (up to six months after diagnosis, and six to 59 months after diagnosis) for patients diagnosed during the most recent calendar period (1986–90).

Results

Table 1 shows characteristics of the 5566 cases included in the analysis. Patients in each deprivation category were broadly similar with respect to morphology, proportion of boys, and the distribution by age and calendar period (data not shown).¶

* The proportion of households headed by a person of social class IV or V is coded at the level of the census ward, and this value assigned to the approximately 10 EDs within each ward.

† The log transformed value of percentage unemployment is used.

‡ Although this analysis is limited to children diagnosed with ALL while living in England and Wales, the distribution of Carstairs scores from which deprivation categories were derived includes EDs for all of the UK (England, Wales, and Scotland) to provide a national standard distribution.

§ Relative survival is the preferred measure of survival in studies among adult cancer patients, because adults can die from causes other than the cancer under study. For children, however, there are few competing causes of death so that crude survival rates are likely to be very close to net survival, and thus may be preferred to relative survival.

¶ In all instances in which data have been cited, but not shown, data are available from the author on request.

Table 1 Characteristics of children (0–14 years) with ALL included in the survival analysis: England and Wales, patients diagnosed 1971–90

	n (%)
Birch and Marsden subcategories	
Acute lymphocytic leukaemia (Ia)*	5452 (98)
Other lymphoid leukaemia (Ib)†	114 (2)
Sex	
Male	3185 (57)
Female	2381 (43)
Age at diagnosis (years)	
Less than 2	601 (11)
2–9	3992 (72)
10–14	973 (17)
Calendar period of diagnosis	
1971–75	1429 (26)
1976–80	1416 (25)
1981–85	1347 (24)
1986–90	1374 (25)
Deprivation category‡	
1 (affluent)	1222 (22)
2	1128 (20)
3	925 (17)
4	943 (17)
5 (deprived)	947 (17)
Unassigned (see text)	401 (7)
Region of residence at diagnosis	
England and Wales	5566 (100)
England	5316 (96)
NHS region	
Northern and Yorkshire	717 (13)
Trent	579 (10)
Anglia and Oxford	591 (11)
North Thames	723 (13)
South Thames	679 (12)
South and West	691 (12)
West Midlands	570 (10)
North and West	766 (14)
Wales	250 (4)

*Includes ICD-O morphology codes 9821, 9824.
†Includes ICD-O morphology codes 9820, 9822, 9823, 9825, 9850.
‡The distribution of cases by deprivation category reflects an increased incidence of ALL among children of higher socioeconomic status, and the inclusion of Carstairs scores for Scottish EDs in the distribution used to generate the quintiles from which the deprivation categories were derived; a disproportionate number of deprived EDs are located in Scotland, so that EDs in England and Wales fall into an upper quintile of the national distribution slightly more than 20% of the time.

The age distribution of cases differed slightly between NHS regions; 76% of cases diagnosed in Wales occurred among children 2–9 years of age, compared with 69% in the North and West region. There were large variations between regions in the proportion of cases in different deprivation categories, reflecting, at least in part, substantial variation between regions in the proportion of the population living in deprived EDs. Thus, whereas 32% of cases diagnosed in the South Thames region were from the most affluent category, in the Northern and Yorkshire region only 15% were from this group, and 27% of patients were from the most deprived category. The sex distribution did not vary between regions.

SURVIVAL

Survival from ALL has increased dramatically over the 20 year period 1971–90 (fig 1). Considerable improvements in survival at one, five, and 10 years after diagnosis are evident for both sexes, and in all three age groups at diagnosis (data not shown).

EFFECT OF DEPRIVATION CATEGORY ON SURVIVAL

Survival at one, five, and 10 years has varied very little between deprivation categories throughout the study period (table 2). Beginning in 1976, the most deprived group had the lowest or next to lowest survival at one, five, and 10 years, however differences in survival between categories did not exceed 10%, and overall survival curves did not differ significantly.

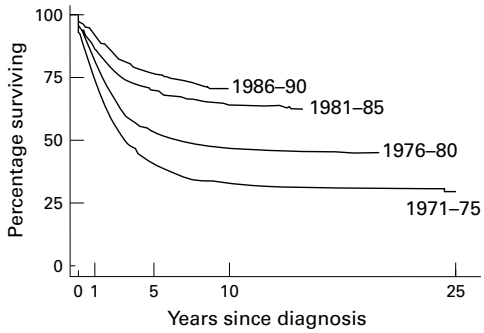

Figure 1 Kaplan-Meier survival estimates for children (aged 0–14) diagnosed with ALL in England and Wales between 1971 and 1990, by calendar period of diagnosis.

EFFECT OF DEPRIVATION CATEGORY ON THE HAZARD OF DEATH

The hazard of death within five years after diagnosis does not differ significantly between deprivation categories after adjustment for sex, single year of age at diagnosis, and NHS region of residence at diagnosis, either over the whole 20 year period, or within any of the five-year calendar periods. For children diagnosed during 1986–90, those in the most deprived group were almost two times more likely to die in the first six months after diagnosis than were children in the most affluent group (hazard ratio, 1.9; 95% CI, 0.9 to 4.0). Although this difference approaches significance ($p = 0.08$) there was not a gradual trend across deprivation categories.

EFFECT OF NHS REGION OF RESIDENCE ON SURVIVAL

Survival at one, five, and 10 years after diagnosis has improved in every NHS region in England and Wales during the 20 year period 1971–90. The extent of improvement has varied by NHS region (table 3). The greatest increase in survival at one year was seen in the West Midlands region, from 70% in 1971–75, the lowest value, to 98% in 1986–90, an increase of 28% (average improvement 8% between successive quinquennia). The same region showed the largest improvement in five-year survival, from 33% to 84% (16% increase between successive quinquennia).** The smallest increase in survival at one year was seen in the North Thames region, and the North and West region; both showed an average increase of only 3% in successive five-year periods, compared with 5.7% for England and Wales as a whole. These two regions also had less than average improvement in five-year survival, with increases of 10% in successive

** When we excluded patients diagnosed in 1971–75 for whom a deprivation category could not be calculated the one year survival estimate for the West Midlands region decreased (from 70% to 66%) and the five-year survival estimate increased only slightly (from 33% to 36%).

Table 2 One, five, and 10 year survival (%) after ALL in childhood (with 95% confidence intervals), by deprivation category and calendar period of diagnosis with mean percentage change in survival between successive five-year calendar periods: England and Wales, patients diagnosed 1971–90

Deprivation category	1 year survival					5 year survival					10 year survival			
	1971–75	1976–80	1981–85	1986–90	Mean % change*	1971–75	1976–80	1981–85	1986–90	Mean % change†	1971–75	1976–80	1981–85	Mean % change‡
1 (affluent)	79 (74, 84)	82 (78, 86)	89 (85, 92)	94 (91, 96)	5.2 (2.9, 7.5)	40 (34, 46)	52 (46, 57)	72 (67, 76)	79 (74, 83)	13.7 (6.5, 20.9)	35 (29, 40)	48 (42, 43)	64 (58, 69)	14.5 (3.5, 25.5)
2	77 (71, 82)	85 (82, 90)	88 (83, 91)	92 (89, 95)	4.7 (0.3, 9.1)	43 (37, 50)	57 (51, 62)	70 (65, 76)	76 (71, 81)	11.2 (5.5, 16.9)	33 (27, 39)	51 (45, 56)	66 (60, 71)	16.5 (5.5, 27.5)
3	72 (66, 78)	81 (75, 85)	89 (84, 92)	94 (90, 97)	7.4 (4.6, 10.2)	44 (37, 51)	51 (45, 57)	72 (66, 77)	78 (72, 83)	12.3 (3.45, 21.1)	34 (27, 40)	43 (37, 49)	64 (58, 70)	15.0 (−29.0, 59.0)
4	82 (76, 86)	82 (77, 87)	84 (79, 88)	94 (90, 96)	3.8 (−3.2, 10.8)	45 (39, 51)	58 (52, 64)	68 (62, 74)	74 (68, 79)	9.7 (4.9, 14.5)	37 (30, 43)	51 (45, 57)	65 (58, 71)	14.0§
5 (deprived)	78 (72, 83)	79 (74, 84)	86 (81, 90)	89 (85, 93)	4.0 (0.7, 7.3)	44 (37, 51)	48 (42, 54)	67 (61, 73)	76 (70, 80)	11.5 (3.2, 19.8)	36 (30, 43)	42 (35, 48)	62 (56, 68)	13.0 (−38.3, 64.3)
Log rank test¶	0.18	0.32	0.44	0.16		0.83	0.10	0.66	0.77		0.78	0.96	0.08	

*Mean percentage change in survival to one year between successive five-year calendar periods; percentage change is significant if confidence intervals do not include zero.
†Mean percentage change in survival to five years between successive five-year calendar periods; percentage change is significant if confidence intervals do not include zero.
‡Mean percentage change in survival to 10 years between successive five-year calendar periods; percentage change is significant if confidence intervals do not include zero.
§Although an increase of 14% is significant, confidence limits cannot be calculated in this instance because the regression line described by these three survival estimates has a standard error of zero.
¶p values for log rank test comparing survival one, five, and 10 years after diagnosis for children in each deprivation category, after excluding cases for whom a deprivation category could not be assigned.

Table 3 One, five, and 10 year survival (%) after ALL in childhood (with 95% confidence intervals), by NHS region of residence and calendar period of diagnosis with mean percentage change in survival between successive five-year calendar periods: England and Wales, patients diagnosed 1971–90

Region of residence at diagnosis	1 year survival					5 year survival					10 year survival			
	1971–75	1976–80	1981–85	1986–90	Mean % change*	1971–75	1976–80	1981–85	1986–90	Mean % change†	1971–75	1976–80	1981–85	Mean % change‡
England and Wales	76 (74, 78)	82 (80, 84)	88 (86, 89)	93 (91, 94)	5.7 (4.9, 6.4)	41 (38, 43)	53 (51, 56)	70 (68, 72)	77 (74, 79)	12.5 (6.8, 18.2)	33 (30, 35)	47 (44, 49)	64 (62, 67)	15.5 (4.5, 26.5)
England	76 (74, 79)	82 (80, 84)	87 (86, 89)	93 (91, 94)	5.4 (5.1, 5.7)	41 (38, 43)	53 (50, 55)	70 (68, 72)	77 (74, 79)	12.5 (6.1, 18.9)	33 (30, 35)	46 (44, 49)	64 961, 67)	15.5 (−2.8, 33.8)
NHS region														
Northern and Yorkshire	71 (64, 77)	82 (75, 87)	86 (80, 91)	94 (89, 96)	7.3 (3.4, 11.2)	37 (30, 45)	53 (45, 60)	70 (63, 76)	80 (74, 85)	14.6 (9.8, 19.3)	30 (23, 37)	44 (36, 51)	67 (59, 73)	18.5 (−14.5, 51.5)
Trent	75 (67, 81)	77 (69, 82)	88 (82, 93)	92 (86, 96)	6.2 (1.1, 11.2)	40 (32, 48)	48 (40, 56)	72 (63, 78)	75 966, 81)	12.9 (1.1, 24.7)	33 (26, 40)	43 (36, 51)	64 (55, 71)	15.5 (−24.9, 55.9)
Anglia and Oxford	74 (66, 80)	85 (79, 90)	85 (78, 90)	90 (84, 94)	4.8 (−1.5, 11.1)	42 (34, 50)	56 (48, 63)	68 (60, 76)	78 (70, 84)	12.0 (9.3, 14.7)	32 (25, 40)	52 (44, 59)	62 (54, 70)	15 (−21.7, 51.7)
North Thames	84 (78, 89)	85 (78, 89)	92 (87, 95)	91 (86, 94)	2.8 (−1.7, 7.3)	49 (42, 56)	60 (41, 67)	76 (70, 82)	77 (71, 82)	10.0 (0.9, 19.1)	42 (35, 49)	55 (47, 63)	70 (63, 76)	14 (6.6, 21.3)
South Thames	76 (69, 81)	80 (74, 85)	92 (87, 95)	95 (90, 98)	6.9 (1.7, 12.1)	34 (27, 41)	46 (39, 53)	72 (64, 78)	79 (64, 78)	16.1 (5.5, 26.7)	26 (19, 32)	42 (34, 49)	65 (57, 71)	19.5 (−6.2, 45.2)
South and West	82 (74, 87)	82 (76, 87)	90 (84, 94)	93 (89, 96)	4.1 (−0.3, 8.5)	49 (41, 57)	52 (45, 59)	78 (71, 83)	73 (66, 79)	9.8 (−7.5, 27.1)	41 (33, 49)	46 (38, 52)	71 (64, 77)	15 (−58.4, 88.4)
West Midlands	70 (61, 76)	79 (71, 85)	79 (72, 85)	98 (93, 99)	8.4 (−2.5, 19.3)	33 (26, 41)	57 (48, 64)	60 (51, 67)	84 (76, 89)	15.6 (2.8, 28.4)	24 (18, 31)	51 (42,58)	54 (46, 62)	15 (−73.0, 103.0)
North and West	79 (73, 84)	86 (80, 90)	86 (79, 90)	89 (84, 93)	3.0 (−1.1, 7.1)	41 (35, 48)	52 (45, 59)	66 (58, 72)	70 (63, 76)	10.1 (3.9, 16.3)	33 (27, 39)	42 (35, 49)	57 (49, 64)	12 (−10.0, 34.0)
Wales	74 (63, 83)	88 (76, 94)	89 (77, 95)	90 (80, 96)	4.9 (−4.8, 14.6)	43 (32, 54)	60 (47, 72)	65 (51, 76)	79 (67, 87)	11.3 (4.6, 18.0)	35 (25, 46)	55 (42, 67)	65 (51, 76)	15 (−21.7, 51.7)
Log rank test§	0.03	0.24	0.01	0.15		0.01	0.25	0.01	0.12		< 0.01	0.15	0.01	

*Mean percentage change in survival to one year between successive five-year calendar periods; percentage change is significant if confidence intervals do not include zero.
†Mean percentage change in survival to five years between successive five-year calendar periods; percentage change is significant if confidence intervals do not include zero.
‡Mean percentage change in survival to 10 years between successive five-year calendar periods; percentage change is significant if confidence intervals do not include zero.
§p values for log rank test comparing survival one, five, and 10 years after diagnosis for children in each deprivation category, after excluding cases for whom a deprivation category could not be assigned.

*Table 4 Hazard of death relative to Anglia and Oxford region (HR), in the first five years after diagnosis with ALL in each NHS region, by calendar period of diagnosis, with mean percentage change in relative hazard between successive periods: adjusted for single year of age at diagnosis, sex, and deprivation category**

	Calendar period of diagnosis									
	1971–75		*1976–80*		*1981–85*		*1986–90*		*Mean percentage change in HR per five-year period (95% CI)*	
NHS region	*Deaths (n)*	*HR (95% CI)*	*Deaths (n)*	*HR (95% CI)*	*Deaths (n)*	*HR (95% CI)*	*Deaths (n)*	*HR (95% CI)*		*p Value†*
Northern and Yorkshire	63	1.07 (0.75, 1.53)	77	1.05 (0.75, 1.46)	54	0.94 (0.62, 1.42)	39	0.84 (0.52, 1.36)	−8.0 (−14.2, −1.8)	0.03
Trent	85	1.10 (0.79, 1.52)	83	1.18 (0.86, 1.63)	37	0.89 (0.57, 1.39)	33	1.03 (0.62, 1.73)	−5.0 (−29.7, 19.7)	0.48
Anglia and Oxford	70	1	72	1	41	1	29	1		
North Thames	86	0.85 (0.62, 1.17)	58	0.88 (0.62, 1.25)	40	0.67 (0.43, 1.03)	46	1.03 (0.64, 1.65)	3.3 (−30.0, 36.6)	0.71
South Thames	114	1.42 (1.05, 1.93)	90	1.29 (0.94, 1.76)	43	0.78 (0.51, 1.20)	31	0.83 (0.50, 1.39)	−22.8 (−53.9, 8.3)	0.09
South and West	65	0.92 (0.65, 1.30)	88	1.04 (0.76, 1.43)	39	0.62 (0.40, 0.96)	49	1.19 (0.75, 1.89)	−3.9 (−51.8, 59.6)	0.79
West Midlands	36	1.30 (0.86, 1.96)	62	0.97 (0.69, 1.37)	63	1.31 (0.88, 1.95)	20	0.62 (0.35, 1.10)	−17.0 (−74.2, 40.2)	0.33
North and West	93	1.05 (0.76, 1.45)	89	1.07 (0.78, 1.47)	56	0.94 (0.63, 1.42)	56	1.51 (0.96, 2.39)	12.5 (−33.0, 58.0)	0.36
Wales	34	0.82 (0.54, 1.26)	18	0.73 (0.43, 1.23)	18	1.15 (0.65, 2.02)	13	1.05 (0.54, 2.03)	11.1 (−20.2, 42.4)	0.27

*Patients for whom a deprivation category could not be assigned are not included in this analysis.
†p value for test of trend in hazard of death over successive five-year calendar periods (1971–75 to 1986–90) within each region, relative to that observed for patients from the Anglia and Oxford region.

*Table 5 Hazard of death relative to Anglia and Oxford region (HR) for children with ALL diagnosed in 1986–90, by time since diagnosis and NHS region: adjusted for single year of age at diagnosis, sex, and deprivation category**

		Time since diagnosis								
		Less than six months			*Six months to five years*			*Overall (up to five years)*		
NHS region	*Children (n)*	*Deaths (n)*	*HR† (95% CI)*	*p Value‡*	*Deaths (n)*	*HR (95% CI)*	*p Value*	*Deaths (n)*	*HR (95% CI)*	*p Value*
Northern and Yorkshire	196	9	0.43 (0.18, 1.06)	0.07	3	1.12 (0.62, 2.04)	0.71	12	0.84 (0.51, 1.36)	0.47
Trent	131	5	0.29 (0.10, 0.87)	0.03	28	1.62 (0.88, 3.01)	0.12	33	1.03 (0.62, 1.73)	0.90
Anglia and Oxford	134	12	1		17	1		29	1	
North Thames	209	12	0.60 (0.27, 1.36)	0.23	34	1.34 (0.74, 2.40)	0.34	46	1.03 (0.64, 1.65)	0.90
South Thames	150	3	0.19 (0.05, 0.70)	0.01	28	1.32 (0.72, 2.42)	0.38	31	0.83 (0.50, 1.39)	0.48
South and West	180	5	0.25 (0.09, 0.73)	0.01	44	1.93 (1.09, 3.40)	0.02	49	1.19 (0.75, 1.89)	0.47
West Midlands	123	3	0.22 (0.06, 0.81)	0.02	17	0.94 (0.48, 1.85)	0.86	20	0.62 (0.35, 1.10)	0.10
North and West	188	17	0.98 (0.45, 2.14)	0.97	39	1.84 (1.03, 3.27)	0.04	56	1.51 (0.96, 2.39)	0.08
Wales	63	3	0.54 (0.15, 1.93)	0.34	10	1.43 (0.65, 3.15)	0.37	13	1.05 (0.54, 2.03)	0.89

*Patients for whom a deprivation category could not be assigned are not included in this analysis.
‡Hazard ratios (HR) are presented as ratios of the death rate in each NHS region to that in Anglia and Oxford (the reference region) during the same interval.
‡p value refers to test comparing hazard of death in each region to that in Anglia and Oxford during the same interval.

five-year periods compared with an average 12.5% for England and Wales as a whole. Survival for patients from the North Thames region was similar to national rates by 1986–90; however, in the North and West region, survival remains lower than in other regions: in 1986–90 one and five-year survival were 4% and 7% lower than the national average respectively. All the regions showed essentially stable or increasing survival between 1981–85 and 1986–90, except the South and West region, where five-year survival fell slightly from 78% to 73%.

EFFECT OF NHS REGION OF RESIDENCE ON HAZARD OF DEATH

The hazard of death within five years of diagnosis of ALL varied substantially for cases residing in some NHS regions compared with that for the Anglia and Oxford region (the reference region), after adjustment for sex, single year of age at diagnosis, and deprivation category (table 4). For example, the hazard of death in the North Thames region was lower, by 15–33%, than that for the reference region for patients diagnosed between 1971 and 1985, but similar (hazard ratio, 1.03) for patients diagnosed during 1986–90. Conversely, patients living in the South Thames region had a 42% higher hazard of death in the early 1970s, but by 1986–90 this had improved to 0.83, 17% below that for patients resident in Anglia and Oxford in the same period. In the North and West region, the hazard of death was similar to Anglia and Oxford until 1985, but rose 1.5-fold (95% CI, 0.96 to 2.39) for patients diagnosed in 1986–90.

Although the five-year hazard of death did not differ greatly between NHS regions for the calendar period 1986–90, patients in most regions had a significantly lower hazard of death than those in Anglia and Oxford in the first six months after diagnosis (table 5). For all regions except the West Midlands, these differences are compensated by excess hazards in the interval between six months and five years after diagnosis. The two regions that do show a significantly greater hazard of death in interval six to 59 months after diagnosis (South and West, and North and West) also show the largest excess hazard over five years, although those five-year excess hazards were not significant (hazard ratios 1.19 and 1.51, respectively).

Discussion

The dramatic improvements in survival described in our study are in keeping with previous studies of crude survival after ALL in the UK since the 1970s.[17 18] This is the first time, however, that national cancer survival data from the National Cancer Registry for England and Wales have been linked with measures of both socioeconomic status and geographical region of residence. Using these measures it becomes possible to disentangle the conjoint

effects of socioeconomic status and area of residence on trends in survival.

Our analysis suggests that the socioeconomic status of a child's family is not a significant determinant of survival after diagnosis with ALL in England and Wales, but that where a child lives within England and Wales may affect his or her chances of survival from this highly curable childhood malignancy, particularly in the first six months after diagnosis.

Differences in survival between socioeconomic groups are small (3–6%) compared with those for some adult cancers studied with the same ecological measure,[1 5] and they do not achieve significance.†† It is noteworthy however, that when small differences do exist, children from the most deprived group are the most disadvantaged. The lack of a significant socioeconomic effect may be interpreted in several ways. It may be that access and use of treatment services related to ALL are similar for children from different strata of society. Alternatively, treatment for ALL may be so effective that small differences between deprivation categories for disease stage at diagnosis, treatment regimen, compliance with treatment, or supportive management may not have a measureable effect on survival. If this were the case, however, we would have expected to see larger differences in survival between deprivation groups in the earlier quinquennia (1971–75, 1976–80) when treatment and management regimens were less effective, but this was not seen.

The regional differences in survival trends over the period 1971–90 suggest either that effective regimens of chemotherapy and supportive care were adopted at different speeds in various NHS regions, and/or that the use of such services by patients resident in different regions has varied over time. The differences in survival between regions appear to wax and wane over the 20 year study period, and largely to resolve for patients diagnosed in 1986–90. There is no evidence of a general north to south gradient in survival, as has been observed in studies of other causes of child morbidity and mortality in England.[29]

The large differences in the socioeconomic composition of the NHS regions within England and Wales made it desirable to conduct an analysis that simultaneously adjusted for both socioeconomic status and NHS region. When we examined the independent effects of socioeconomic status and region of residence, only two of the eight English regions or Wales had a significantly different five-year hazard of death in any one of the five-year calendar periods, 6%, no more than might be expected by chance. Nonetheless, divergent trends in the adjusted hazard rates in some regions suggest that there are some unmeasured factors affecting survival in different regions, or that using the Carstairs index to adjust for socioeconomic status does not adequately control for this variable. This is supported by the finding that for the most recent period, 1986–90, the hazard of death in most regions differed significantly from that of the reference region in the first six months after diagnosis. Factors which could underlie either regional or socioeconomic differences in survival include white blood cell count at diagnosis, compliance with chemotherapy, nutritional status, and the distributions of cellular subtypes with different prognoses.[10–12 30–32] It is also possible that chemotherapeutic protocols used in some regions are associated with differing degrees of short term toxicity, or that regional differences in the management of complications of treatment contribute to these observed differences in the risk for death in the first six months after diagnosis. Unfortunately, there is no information on any of these factors in this national cancer registry dataset.

The Carstairs index has not been widely used to study differentials in survival among children, and is worthy of comment. First, the Carstairs index may not be a valid measure of the socioeconomic milieu experienced by children, and the accuracy with which the census level variables composing the Carstairs index reflect socioeconomic status may vary over time and place. Second, heterogeneity in the socioeconomic status of children within an ED may have obscured measurable differences between deprivation categories. Despite these potential limitations, the Carstairs index provides an invaluable way of exploring the relation between socioeconomic status and survival in this national dataset, because none of the children in our dataset had social class recorded. Socioeconomic gradients have been demonstrated for other childhood health outcomes using similar areal measures of deprivation,[33–35] so it seems reasonable to assume that it would be possible to demonstrate a gradient for survival from ALL in children using the Carstairs index, should such a gradient exist.

Although the National Cancer Registry for England and Wales provides an almost complete record of cancer survival in the entire population of England and Wales, it is possible that variations in regional cancer registry practices may have produced an artefactual effect, or hidden actual differences; a national, standardised system for cancer registrations would go far towards reducing the potential distortion of national data introduced by the disparate practices of regional cancer registries.

To unravel the reasons for the observed regional variation in survival after ALL, secular trends within NHS regions could be examined in relation to the establishment of regional paediatric oncology services, and enrollment in UKALL trials. As health service administrative regions, NHS regions are a useful unit of analysis with which to investigate questions about access to health services, but they do not provide insight into the other means by which

†† A lack of significance may be considered less important in a population based study such as this one than in a study that derives a sample from some larger population. Although variations in the case ascertainment, follow up, and reporting practices of different cancer registries may have introduced some bias, the differences in survival observed in this population based data may be considered to reflect the actual survival experience of children diagnosed with ALL in England and Wales in 1971–90.

residence in a given region may exert an influence on survival, and further measures of regional effect are needed. Survival after diagnosis with other, less treatable, forms of childhood cancer in the UK should also be examined for socioeconomic gradients and regional variation.

This study was conducted as part of a larger project examining the influence of geographical region, socioeconomic status, and morphology on cancer survival in England and Wales, funded by the Cancer Research Campaign, grant number SP2381/0101. Decades of meticulous dedication to their work by the staff of regional cancer registries across England and Wales have made this national study possible. We gratefully acknowledge the work of all these staff, and the expert advice and assistance of P Babb and J Jones (Office for National Statistics), A Pitard and C Brandon-Jones (Cancer and Public Health Unit), C Stiller (Childhood Cancer Research Group, Oxford, UK), and J Estève (International Agency for Research on Cancer (IARC), Lyon, France).

1 Schrijvers CTM, Mackenbach JP, Lutz J, Quinn MJ, Coleman MP. Deprivation, stage at diagnosis, and cancer survival. *Int J Cancer* 1995;**63**:324–9.
2 Kogevinas M, Marmot MG, Fox AJ, Goldblatt PO. Socioeconomic differences in cancer survival. *J Epidemiol Community Health* 1991;**45**:216–19.
3 MacKie RM, Hole DJ. Incidence and thickness of primary tumours and survival of patients with cutaneous malignant melanoma in relation to socioeconomic status. *BMJ* 1996; **312**:1125–8.
4 Schrijvers CTM, Mackenbach JP. Cancer patient survival by socioeconomic status in the Netherlands: a review for six common cancer sites. *J Epidemiol Community Health* 1994; **48**:441–6.
5 Schrijvers CTM, Mackenbach JP, Lutz J, Quinn MJ, Coleman MP. Deprivation and survival from breast cancer. *Br J Cancer* 1995;**72**:738–43.
6 Sant M, Capocaccia R, Verdecchia A, *et al*. Survival of women with breast cancer in Europe: variation with age, year of diagnosis and country. The EUROCARE Working Group. *Int J Cancer* 1998;**77**:679–83.
7 Cancer Research Campaign. *Trends in cancer survival in Great Britain. Cases registered between 1960 and 1974.* London: Cancer Research Campaign, 1982.
8 Karjalainen S. Geographical variation in cancer patient survival in Finland: chance, confounding, or effect of treatment? *J Epidemiol Community Health* 1990;**44**:210–14.
9 Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J. *Survival of cancer patients in Europe: the EUROCARE study.* IARC Scientific Publications No. 132. Lyon: International Agency for Research on Cancer, 1995.
10 McWhirter WR, Smith H, McWhirter KM. Social class as a prognostic variable in acute lymphoblastic leukaemia. *Med J Aust* 1983;**2**:319–21.
11 Petridou E, Kosmidis H, Haidis S, *et al*. Survival from childhood leukemia depending on socioeconomic status in Athens. *Oncology* 1994;**51**:391–5.
12 Oakhill A, Mann JR. Poor prognosis of acute lymphoblastic leukaemia in Asian children living in the United Kingdom. *BMJ* 1983;**286**:839–41.
13 Novakovic B. U.S. childhood cancer survival, 1973–1987. *Med Pediatr Oncol* 1994;**23**:480–6.
14 Expert Advisory Group on Cancer. *A policy framework for commissioning cancer services.* London: Department of Health, 1995.
15 Stiller CA. Centralisation of treatment and survival rates for cancer. *Arch Dis Child* 1988;**63**:23–30.
16 Stiller, CA, Draper GJ. Treatment centre size, entry to trials, and survival in acute lymphoblastic leukaemia. *Arch Dis Child* 1989;**64**:657–61.
17 Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. *Br J Cancer* 1990;**62**: 806–15.
18 Stiller CA. Population based survival rates for childhood cancer in Britain, 1980–91. *BMJ* 1994;**309**:612–16.
19 OPCS. *Review of the national cancer registration system—England and Wales.* Series MB1 no. 17. London: HMSO, 1990.
20 American Cancer Society. *Manual of tumor nomenclature and coding.* Washington, DC: American Cancer Society, 1951.
21 World Health Organisation. *International classification of diseases for oncology.* Geneva: World Health Organisation, 1976.
22 Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer* 1987;**40**:620–4.
23 Carstairs V, Morris R. Deprivation and mortality: an alternative to social class? *Community Medicine* 1989;**11**: 210–19.
24 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958;**53**:457
25 Statacorp. *Stata statistical software: release 5.0*. Texas: Stata Corporation, 1997.
26 Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J Royal Stat Soc* 1972;**135**:185–207.
27 Draper GJ, Bower BD, Darby SC, Doll R. Completeness of registration of childhood leukaemia near nuclear installations and elsewhere in the Oxford region. *BMJ* 1989;**299**: 952.
28 Wilson S, Bell CMJ, Black RJ, *et al.* Health care system, cancer registration and follow-up of cancer patients in the United Kingdom. In: Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J, eds. *Survival of cancer patients in Europe: the EUROCARE study.* IARC Scientific Publications No. 132. Lyon: International Agency for Research on Cancer, 1995:71–4.
29 OPCS. *The health of our children*. Series DS No. 11. London: HMSO, 1995.
30 Viana M, Murao M, Ramos G, *et al*. Malnutrition as a prognostic factor in lymphoblastic leukaemia: a multivariate analysis. *Arch Dis Child* 1994;**71**:304–10.
31 Davies HA, Lennard L, Lilleyman JS. Variable mercaptopurine metabolism in children with leukaemia: a problem of non-compliance. *BMJ* 1993;**306**:1239–40.
32 Ramot B. Hypothesis: the environment is a major determinant of the immunological sub-type of lymphoma and acute lymphocytic leukaemia in children. *Br J Haematol* 1982;**52**:183–9.
33 Spencer N, Logan S, Scholey S, Gentle S. Deprivation and bronchiolitis. *Arch Dis Child* 1996;**74**:50–2.
34 Jones CM, Taylor GO, Whittle JG, Evans D, Trotter DP. Water fluoridation, tooth decay in 5 year olds, and social deprivation measured by Jarman score: analysis of data from British dental surveys. *BMJ* 1997;**315**:514–17.
35 Bisset AF, Russell D. Grommets, tonsillectomies and deprivation in Scotland. *BMJ* 1994;**308**:1129–32.