

Leukaemia incidence near coastal features

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Abstract

Background The aim of the study was to independently test the hypothesis that leukaemia incidence is higher in proximity to estuaries.

Methods Electoral wards were classified as to whether they included estuarine, coastal or only inland features. Rates of different adult and childhood leukaemias were computed for each ward category; that is, acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) aged 0–79 and for all childhood leukaemias combined (aged 0–14).

Results Poisson regression analysis controlling for the effects of sex, age, and socioeconomic and urban–rural status, showed no statistically significant differences in incidence between wards with different levels of estuarine classification.

Conclusion The hypothesis created from an earlier dataset that a link exists between leukaemia and residence near estuaries is not upheld.

Keywords: leukaemia incidence, estuaries, acute lymphoblastic leukaemia, acute myeloid leukaemia

Introduction

Apart from the established leukaemogenic effect of ionizing radiation, little is known about the aetiology of leukaemia in adults or children. For many years there has been interest in the geographical distribution of leukaemia occurrence. In a search for possible aetiological clues, such work has usually involved identifying clusters or areas of raised incidence, particularly in children, and has focused on two possibilities: an infectious process,^{1–3} or the effects of localized environmental pollution, especially radiation exposure or proximity to nuclear installations.^{4,5} One study suggested an association between raised leukaemia incidence and proximity to estuaries.⁶ This has plausibility, as there is evidence of increased radiation levels very largely from naturally occurring sources in estuarine silts, and it is possible that exposure to ionizing radiation from heavy metals such as uranium might have leukaemogenic and/or carcinogenic effects. However, the association arose from a limited study of only 3 years of incidence data, and the hypothesis requires testing on a larger, independent dataset. This was the objective of our study.

Materials and methods

Patient and population data

Incidence data were obtained from the Leukaemia Research Fund (LRF) Data Collection Study (DCS), a large specialist registry of leukaemias and lymphomas, which has been collecting high-quality population-based incidence data on haematological diseases since 1984. At its beginning this population-based registry covered approximately 40 per cent of the population of England and Wales, but since 1988 the number of areas contributing data has been reduced following rationalization to make them co-terminous with areas in which other detailed epidemiological studies are being carried out.^{7,8} The population involved is currently approximately 12 million. The DCS collects data on newly diagnosed cases of all ages and receives direct notifications from the diagnostic laboratories of collaborating haematologists and histopathologists. Clerical officers employed by the LRF centre collect and record information on every new case of leukaemia, lymphoma and other myeloproliferative and lymphoproliferative conditions, including patient's full name, sex, date of birth, their home address with the postcode at the time of diagnosis, the diagnosis itself and the date on which it was made. All data are recorded on standard forms and sent with copies of relevant haematological and histopathological reports to the LRF centre in Leeds. Cases are not registered unless there is a valid haematological or histopathological report. Data are regularly cross-checked with other regional cancer registries and, for childhood haematological neoplasms, the National Registry of Childhood Tumours (maintained by the Childhood Cancer Research Group, Oxford). As a consequence of these stringent measures, in a comparison study with other cancer registries, the LRF data were estimated as being close to 92.4 per cent complete.⁹

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At the time of this analysis, the latest year for which data have been completely validated and cross-checked was 1993. As the original hypothesis that this study seeks to test was based on DCS incidence data from the years 1984–1986, we used cases diagnosed in the period 1987–1993 to provide an independent dataset covering the longest possible period for hypothesis testing. Cases in the age range 0–79 years were used; older cases were excluded to avoid possible under-ascertainment. Relevant information for each case included diagnosis, age at diagnosis, sex and electoral ward of home address at diagnosis.

Population denominators, by sex and 5 year age groups, were obtained from the 1991 Census estimates for the electoral wards in the areas covered by the DCS. The data area encompassed 3852 wards from 25 counties, not all of which contributed cases to the DCS for the whole time period. Total person-years were calculated by multiplying the population of a given ward by the number of years the ward was included in the study.

Each electoral ward was classified according to its proximity to an estuary or a coast, or whether the ward was entirely inland. The classification used was that developed by the authors of the original report; an estuary is defined as a semi-enclosed coastal body of water reaching from the mouth of the river to the lower tidal reaches.⁶ Estuaries were divided into three parts: areas with a substantial amount of mud (as marked on the Ordnance Survey maps), the mouth of the river without mud and the tidal reaches of the river that do not contain mudflats. Consequently, wards were classified into five categories: (1) mud; (2) mouth; (3) tidal; (4) other coastal; (5) inland.

Wards were classified into one of six categories ranging from wholly urban to wholly rural, based on the percentage of enumeration districts (EDs), the building blocks of electoral wards, classified as urban in each ward (Table 1). This follows the scheme used by Office for National Statistics for the 1981 Census, and an ED was classed as urban if its population density was 25 people per hectare or higher.¹⁰ Following the scheme originally used by Alexander *et al.*⁶ wards were also grouped into two divisions: urban (50 per cent or more of EDs were urban) and rural (less than 50 per cent of EDs were urban).

The socio-economic status of each ward was assessed using the Townsend index,¹¹ which is a composite score based on four Census variables (unemployment, car ownership, home ownership, overcrowding). The Townsend index is an established indicator of material deprivation, which has been shown to perform well in studies attempting to explain geographical variations in health.¹² Wards were classified into five categories containing roughly similar-sized populations, with level 1 being wards of highest socio-economic status (lowest Townsend score) and level 5 being wards of lowest socio-economic status (highest Townsend score).

Statistical methods

Incidence rates were calculated as annual rates per 100 000 person-years, directly standardized (using sex and 5 year age groups) to the European population.

Using Poisson regression, with the electoral ward stratified by age and sex as the unit of observation, an ecological analysis was conducted to examine the relationship between leukaemia incidence and proximity to estuaries, with adjustment for the effects of age (5 year age groups), sex and ward characteristics (Townsend score and urban–rural classification) known to influence leukaemia risk. Model 1 used the five-level estuarine classification of wards (mud, mouth, tidal, coastal, inland); model 2 used a three-level classification (estuarine, coastal, inland); and model 3 used a two-level classification (not inland, inland). The models were examined and compared with the null model, which contained factors for age, sex, urban–rural status (two levels) and Townsend score (five levels) only. This null model was used because of the original work in this area⁶ but also because of the body of work from the LRF centre, which shows that age, sex, deprivation and urban–rural status are all important in the distribution of leukaemia cases. This is a conservative approach and is tested against the *a priori* assumption that any of the coastal features could be important. The urban–rural effects were tested against coastal features and shown to have low correlations, and the statistical significance of the estuarine classification used was assessed using the likelihood ratio test, which is distributed as χ^2 . The statistical software package used was Stata.¹³

Using cases aged 0–79 years, separate analyses were carried out for acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) and combined leukaemias (ALL + AML + CML), as well as for childhood leukaemias (combined leukaemias aged 0–14 years). Chronic lymphocytic leukaemia was not used in the analysis because of its close biological links with the lymphomas (rather than these leukaemias).

Results

Table 1 shows the number of wards classified according to urban–rural status, socioeconomic status and estuarine classification: of a total of 3852 wards in the study area, the majority were urban (2799) or classed as inland (3013), with only 54 wards classed as mouth and 101 wards classed as tidal. The total number of combined leukaemias (ALL + AML + CML) in the study area was 3581, including 983 ALL, 1870 AML and 728 CML, and there were 677 childhood leukaemias. For each of the diagnostic groups analysed, Table 1 also shows the number of cases diagnosed according to the ward classification. For the mouth and tidal ward categories the number of cases was small, falling below 20 for ALL (mouth wards), CML (mouth and tidal wards) and childhood leukaemias (mouth and tidal wards).

Table 2 shows directly standardized incidence rates for each of the disease groups according to the estuarine classification of the ward. No clear trend in incidence was apparent with estuarine classification, although tidal or coastal wards appeared to have the highest incidence for most diagnostic groups.

Table 1 Number of cases of acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), combined leukaemias (ALL + AML + CML) and childhood leukaemias diagnosed in the period 1987–1993 in parts of the United Kingdom, by ward classification

	Number of wards	Cases aged 0–79 years				Cases aged 0–14 years
		ALL	AML	CML	Combined leukaemias	Childhood leukaemias
Total number of cases	3852	983	1870	728	3581	677
<i>Urban–rural status: % of EDs in ward defined as urban</i>						
Urban						
100	2097	636	1216	448	2300	434
75–99	450	138	255	101	494	100
50–74	252	52	81	35	168	33
25–49	96	15	33	15	63	14
Rural						
1–24	47	5	21	6	32	3
0	910	137	264	123	524	93
<i>Socio-economic status: Townsend level</i>						
1 (highest)	1057	176	361	153	690	114
2	852	184	356	139	679	118
3	689	191	341	146	678	128
4	609	174	323	133	630	122
5 (lowest)	645	258	489	157	904	195
<i>Estuarine classification</i>						
Mud	427	119	214	89	422	62
Mouth	54	15	37	11	63	8
Tidal	101	25	43	13	81	17
Coastal	257	59	153	62	274	38
Inland	3013	765	1423	553	2741	552

Table 2 Acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), combined leukaemias (ALL + AML + CML) and childhood leukaemias diagnosed in the period 1987–1993 in parts of the United Kingdom, standardized incidence rates* per 100 000 person years

Ward classification	Cases aged 0–79 years				Cases aged 0–14 years
	ALL	AML	CML	Combined leukaemias	Childhood leukaemias
Estuarine					
Mud	1.24	1.79	0.76	3.80	3.32
Mouth	1.05	2.03	0.63	3.71	3.03
Tidal	1.25	1.81	0.54	3.59	4.13
Coastal	1.21	2.14	0.85	4.20	4.07
Inland	1.16	1.78	0.72	3.66	3.97

*Rates directly standardized using European population.

Poisson regression analysis showed that, after controlling for the effects of age, sex, urban–rural status and socioeconomic status, there was no statistically significant difference in incidence between wards at different levels of estuarine classification ($p > 0.05$, likelihood ratio test, Table 3). (Inclusion of urban–rural status and socioeconomic status, variables known to affect the incidence of leukaemia, improved the fit of the regression model, but the improvement was not statistically significant.) Although the overall effect of estuarine ward classification on incidence was not formally significant, incidence rate

ratios for AML, CML and the combined leukaemias were all highest in coastal wards (incidence in inland wards used as the reference level, models 1 and 2, Table 3); and for all diagnostic groups except childhood leukaemias incidence was higher in wards classed as not inland (model 3, Table 3).

Discussion

This study suffers from the limitations of all ecological regression studies that examine associations between exposures and

Table 3 Acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), combined leukaemias (ALL + AML + CML) and childhood leukaemias diagnosed in the period 1987–1993 in parts of the United Kingdom, incidence rate ratios by estuarine classification of ward

Estuarine classification	Cases aged 0–79 years						Cases aged 0–14 years					
	ALL		AML		CML		Combined leukaemias		Childhood leukaemias		Childhood leukaemias	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
<i>Model 1</i>												
Mud	1.13	0.93–1.37	1.00	0.87–1.15	1.07	0.85–1.34	1.05	0.95–1.16	0.84	0.64–1.10	0.84	0.64–1.10
Mouth	0.95	0.57–1.59	1.07	0.77–1.49	0.88	0.49–1.61	1.01	0.78–1.29	0.75	0.37–1.51	0.75	0.37–1.51
Tidal	1.09	0.73–1.62	0.99	0.73–1.33	0.76	0.44–1.32	0.97	0.78–1.21	1.04	0.64–1.69	1.04	0.64–1.69
Coastal	1.04	0.80–1.36	1.15	0.98–1.37	1.21	0.93–1.58	1.14	1.01–1.29	1.00	0.72–1.40	1.00	0.72–1.40
Inland	1	—	1	—	1	—	1	—	1	—	1	—
<i>p</i>	0.79		0.56		0.47		0.31		0.66		0.66	
<i>Model 2</i>												
Estuarine	1.10	0.93–1.31	1.01	0.89–1.14	1.00	0.82–1.23	1.03	0.94–1.13	0.87	0.69–1.09	0.87	0.69–1.09
Coastal	1.04	0.80–1.36	1.16	0.98–1.37	1.21	0.93–1.58	1.14	1.01–1.29	1.00	0.72–1.40	1.00	0.72–1.40
Inland	1	—	1	—	1	—	1	—	1	—	1	—
<i>p</i>	0.52		0.25		0.38		0.11		0.44		0.44	
<i>Model 3</i>												
Not inland (estuarine + coastal)	1.09	0.94–1.26	1.05	0.95–1.17	1.07	0.90–1.27	1.06	0.99–1.15	0.90	0.74–1.10	0.90	0.74–1.10
Inland	1	—	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
<i>p</i>	0.28		0.34		0.45		0.11		0.30		0.30	

IRR, incidence rate ratio, after controlling for effects of age, sex, urban–rural classification and Townsend score of ward. *p* indicates significance of likelihood ratio test, compared with null model (age, sex, urban–rural, Townsend score).

outcomes that have been measured at a group rather than an individual level. Errors can result from the assumption that characteristics used to describe an area accurately describe the exposures of individuals in that area. For example, a ward was classed as estuarine or coastal if any of its boundaries had contact with the relevant coastal feature, regardless of the actual geographical distribution of the population within the ward, some or none of which may actually have been located near the coastal feature in question. Such misclassification, together with omission from the model of relevant factors, may result in loss of power, and despite inclusion in our models of variables representing the effects of age, sex, urban-rural classification and socioeconomic status, all of which are known to be associated with leukaemia risk, none of the models explained a high proportion of the geographical variation in incidence in our data.

Our objective was to test the hypothesis, first reported in 1990, of an association between raised leukaemia incidence and proximity to coastal features.⁶ Since then, a further two studies have been published: one found an evenly distributed excess of childhood ALL in 1974–1976 in a narrow 3 mile strip along the east coast of Ireland,¹⁴ whereas the other was a study of adult acute leukaemia diagnosed in 1981–1994 in East Anglia and also reported an estuarine excess.¹⁵

Our study was based on a larger number of cases, collected over a much wider area, and used a larger geographical unit of analysis (wards) than the East Anglian study, which used postcode districts. Because population denominators were not available for postcode districts, Badrinath *et al.*¹⁵ used a case-control approach to estimate the number of leukaemia cases expected in each district, taking non-haematological malignancies as their controls. This relies on the assumption that the geographical distribution of non-haematological malignancies is representative of that of the general population, which, given the known geographical heterogeneities in cancer incidence and mortality, may not be true.^{16–18} These differences in technique may account for the different conclusions of their study compared with our own.

The study in Ireland¹⁴ examined childhood ALL mortality over the period 1971–1982 and incidence over the period 1974–1983. As in our own study, no significant geographical variation overall was found, and rates in coastal areas were similar to rates inland, with the distribution of high rates appearing random over the country. However, finer subdivision of the time period revealed a significantly raised incidence along the east coast in the years 1974–1976 only, which the authors were unable to explain.

The original study by Alexander *et al.*⁶ recognized that there were no definite ecological or biological pathways by which exposure to leukaemogenic agents such as heavy metals or radionuclides might be elevated in areas near coastal features, and that might explain the raised leukaemia incidences they found, and concluded that their findings needed independent confirmation before any interpretation was possible. We used incidence data from the same specialist registry and employed

the same estuarine classification of wards as used by Alexander *et al.*, but based our analyses on cases diagnosed in 1987–1993, the longest available time period that was independent from their original study. Whereas Alexander *et al.* found significantly raised risks for leukaemias (ages 0–84 years) in estuarine areas (relative risk 1.09) and reduced risks in coastal areas (relative risk (RR) = 0.83) compared with inland areas, we found, using a larger dataset collected over a longer time period, no significant associations with estuarine classification and leukaemia incidence for any of the disease or age groups examined, although for the age group 0–79 years incidence of all leukaemias combined was raised in coastal wards compared with inland wards (incidence rate ratios: estuarine = 1.03, coastal = 1.14).

In conclusion, although some coastal or estuarine wards, when aggregated, give slightly higher leukaemia incidence rates than inland wards, none were significant, and we were unable to confirm the association first postulated by Alexander *et al.* in 1990.

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References

- 1 Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukaemia. *Leukaemia* 1988; **2**: 120–125.
- 2 Kinlen LJ, Clarke K, Hudson C. Evidence from population mixing in British New Towns 1946–1985 of an infectious basis for childhood leukaemia. *Lancet* 1990; **336**: 577–582.
- 3 Alexander FE. Viruses, clusters and clustering of childhood leukaemia: a new prospective? *Eur J Cancer* 1993; **29A**: 1424–1443.
- 4 Cook-Mozaffari PJ, Darby SC, Doll R, *et al.* Geographical variations in mortality from leukaemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969–1978. *Br J Cancer* 1989; **59**: 476–485.
- 5 Bithell JF, Dutton SF, Draper GJ, Neary NM. Distribution of childhood leukaemias and non-Hodgkin's lymphomas near nuclear installations in England and Wales. *Br Med J* 1994; **309**: 501–505.
- 6 Alexander FE, Cartwright RA, McKinney PA, Ricketts TJ. Leukaemia incidence, social class and estuaries: an ecological analysis. *J Publ Hlth Med* 1990; **12**: 109–117.
- 7 Cartwright RA, Alexander FE, McKinney PA, Ricketts TJ. *Leukaemia and lymphoma. An atlas of distribution within areas of England and Wales 1984–1988*. London: Leukaemia Research Fund, 1990.
- 8 Cartwright RA, McNally RJQ, Rowland DJ, Thomas J. *The descriptive epidemiology of leukaemia and related conditions in parts of the United Kingdom 1984–1993*. London: Leukaemia Research Fund, 1997.
- 9 Alexander FE, Ricketts TJ, McKinney PA, Cartwright RA. Cancer registration of leukaemias and lymphomas: results of a comparison with a specialist registry. *Community Med* 1988; **11**: 81–89.

- 10 Craig J. *An urban-rural categorisation for wards and local authorities*. London: HMSO, 1982.
- 11 Townsend P, Phillmore P, Beattie A. *Health and deprivation: inequality and the north*. London: Croom Helm, 1988.
- 12 Morris R, Carstairs V. Which deprivation? A comparison of selected deprivation indices. *J Publ Hlth Med* 1992; **13**: 318-326.
- 13 StataCorp. *Stata statistical software: Stata user's guide release 5*. New York: Stata Press, 1997.
- 14 Herity B, Daly L, Breatnach F, *et al*. Childhood leukaemia in Ireland. *Irish Med J* 1992; **85**: 50-52.
- 15 Badrinath P, Day NE, Stockton D. Geographical clustering of acute adult leukaemia in the East Anglian region of the United Kingdom: a registry-based analysis. *J Epidemiol Commun Hlth* 1999; **53**: 317-318.
- 16 Gardner MJ, Winter PD, Taylor CP, Acheson ED. *Atlas of cancer mortality in England and Wales 1968-1978*. New York: John Wiley, 1983.
- 17 Smans M, Muir CS, Boyle P. *Atlas of cancer mortality in the European Economic Community*. IARC Scientific Publications No. 107. Lyon: IARC, 1992.
- 18 Swerdlow A, dos Santos Silva I. *Atlas of cancer incidence in England and Wales 1968-1985*. Oxford: Oxford University Press, 1993.

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