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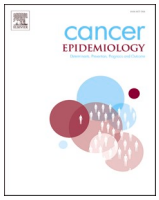

Epidemiology of acute lymphoblastic leukaemia in Sardinia, Italy: Age, sex, and environmental correlates

Giorgio Broccia [a], Jonathan Carter [b], Cansu Ozsin-Ozler [c], Sara De Matteis [d], Pierluigi Cocco [e,*]

[a] Department of Haematology and Bone Marrow Transplants, Hospital A. Businco, Cagliari 09121, Italy
[b] University of Coventry, Coventry CV1 5FB, United Kingdom
[c] Hacettepe University, Faculty of Dentistry, Department of Pediatric Dentistry, Ankara, Turkey
[d] Department of Health Sciences, University of Milan, Italy
[e] Centre for Occupational and Environmental Health, Division of Public Health, Health Services Research &Primary Care, University of Manchester, Manchester M13 9PL, United Kingdom

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ABSTRACT

Using a database of 1974–2003 incident cases of haematological malignancies, we explored the time trend, geographic spread and socio-economic and environmental correlates of ALL incidence in Sardinia, Italy, by sex and age. The age- and sex-standardized (World population) ALL incidence rate was 2.0 per 100,000 (95% CI 1.8 – 2.1) and showed variable trend patterns by sex and age. In the total population, ALL incidence showed an annual per cent change of −1.4% (95% CI -0.59 – -3.34) over the study period, with a knot separating a downward slope in 1974–1996 from an increase in 1996–2003. ALL incidence replicated such pattern in women but not men, whose incidence did not substantially vary over the study period (APC = −2.57%, 95% CI -5.45 – 0.26). Among women, the spatial analysis suggested a clustering of ALL in the southwestern part of the region, whilst only a commune had a high posterior probability of a high ALL incidence among men. Three unrelated communes showed a high posterior probability of ALL at age ≤ 24; only the most populated urban centre showed excess cases at age ≥ 25 years. There was no correlation between the geographic spread of ALL at ages ≤ 24 and ≥ 25 years (p = 0.082). Urban residence was a risk factor for the younger age group. Residences near industrial settlements and in the most populated urban centre were risk factors for subjects aged ≥ 25 years. Our findings suggest age-related differences in ALL aetiology.

1. Introduction

Acute lymphoblastic leukaemia (ALL) is a malignancy of lymphoid cells at an early stage of their differentiation process that spreads in the blood and invades the bone marrow and other sites. [1] The aetiology of childhood ALL includes a variety of congenital conditions, such as Down syndrome, hereditary and acquired genetic mutations, and lifestyle, occupational, and environmental exposures, such as smoking, ionizing radiation, benzene, formaldehyde, insecticides, herbicides, as well as chemical exposures experienced by both parents before conception and by the mother during pregnancy and, for the adult forms, by the individuals throughout their life. [2] Multiple conditions, including pre-existing diseases, chemotherapeutic, and infectious agents, have also been proposed. [2] The International Agency for Research on Cancer has classified seven occupational agents as certain human carcinogens targeting the haemolymphatic system, namely: 1–3 butadiene, benzene, coal tar pitch, x and γ radiation, formaldehyde, lindane, and pentachlorophenol. [3] Consistently with the multiple conditions and agents shown to affect risk, multistage, multifactorial carcinogenetic processes have been proposed. [2] ALL incidence peaks in the first five years of life, sharply decreases with age, reaches its lowest between 25 and 44 years, and shows a modest increase afterwards. [1] Studies on environmental exposures have mainly focused on childhood forms [4–7] as the rarity of the disease has seldom allowed investigating ALL specifically among adults. Two studies, one from the U.S.A. [8] and another from New Zealand, [9] reported contrasting results on ALL risk among electrical occupations, while the role of occupational exposure to benzene is uncertain. [10] A case-control study conducted in the U.S.A.

* Correspondence to: Centre for Occupational and Environmental Health, Division of Population Health, Health Services Research & Primary Care, University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom.
E-mail address: pierluigi.cocco@manchester.ac.uk (P. Cocco).

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described an elevated risk associated with work in plastics manufacturing and any job using explosives. [11] HTLV-1 infection, which is endemic in Africa, South America and Australia, [12,13] is the cause of adult cases of acute T cell leukaemia, which would suggest a role of infectious agents, consistent with some epidemiological studies and the herd immunity hypothesis about the time and space clustering of childhood forms. [14,15] Besides, the observed protective effect from early contact with pets and livestock [16] supports a contribution by the development of immune competence as speculated more than three decades ago. [17] Polymorphisms in genes implicated in the metabolism of xenobiotics and gene repair, such as CYP2E1, GSTM1, NQO1, NAT2, MDR1, and XRCC1, might modulate ALL risks associated with environmental exposures, such as pesticides, smoking, trihalomethanes, and ionizing radiation at all ages. [18] However, GSTM1 and GSTT1 polymorphisms did not show an association with adult ALL in one study, [19] whilst the GSTM1 and GSTT1 null genotypes were more frequent among male ALL cases aged $\leq$ 30 years in another study. [20] Such findings suggest that the ability to metabolize xenobiotics, and therefore the role of environmental factors, might be relevant for some but not all cases. Also, the extent of aetiologic heterogeneity between the ALL subtypes, such as precursor acute B-and T-cell leukaemia and T-cell leukaemia, and within each subtype by age at occurrence is still unclear. [21] Although the few studies on adult ALL do not allow to confirm or discard any hypothesis, childhood and adult forms of ALL might differ by the pattern of concurrent etiological factors and, perhaps, histological subtype.

The existing descriptive epidemiology studies would not help since, in most instances, they explored the incidence and geographic distribution of childhood ALL cases or all ages combined, at most broken down by sex. In the United Kingdom, the 2004–2009 age-adjusted incidence rate of ALL (all forms) was 1.6 (1.4 – 1.7)/100,000, and it was prevalent among men. [22] 1999–2008 age-standardized rates were lower among adults in the U.S.A. state of Georgia (0.8/100,000). [23] Globally, from 1990 to 2017, ALL incidence has been increasing in 55 countries, remaining stable in 29, and decreasing in 111 countries. [24] A slight upward trend in ALL incidence (all ages) was observed in Denmark, [25] and China, where a geographic variation across the Shanghai area districts was also reported. [26] In a previous paper, we described a slightly increasing incidence of childhood ALL with a few clusters scattered across the island of Sardinia, Italy. [27] To understand differences and similarities in the epidemiology of childhood and adult ALL, we explored the time trend and the geographical distribution of ALL incidence (International Classification of Diseases 10th Revision (ICD-10) codes: C91.0, C91.3, C91.5, C91.6) [28] and its relationship with several plausible environmental risk factors by age.

2. Material and methods

2.1. Study population

The database of haemolymphatic cancer used for this analysis was previously described [29] and validated by comparison with mortality and hospitalization data [30] and Cancer Registry records. [31] The total records were 14,744. After excluding 202 cases of uncertain diagnosis, the cases of ALL (all forms) were 786, 326 women and 460 men, comprising 400 cases in paediatric age ($\leq$ 14 years) who were the object of a separate paper. [27] Residence at the time of diagnosis was missing for 15 cases (2.0%) who contributed to the prior age- and sex-specific regional rates but not to the geographic analysis nor the association with environmental risk factors. We had access to the anonymous records grouped by sex, 10-year age group, residence, diagnosis, and year of diagnosis but not to pathological, clinical, and bio-molecular information.

2.2. Statistical methods

For each of the 356 Sardinian administrative units (or communes as in the Italian definition) existing in 1974, we calculated the annual incidence rate of ALL along the study period over the total study population indirectly standardized by applying the 1974–2003 regional rates specific for each 10-year age and sex group to the corresponding strata of the local population. For the total regional population, by sex, and separately for the 0–24 and the 25+ years age groups, we calculated standardized rates by applying the age- and sex-specific 1974–2003 regional rates to the corresponding strata of the Standard World population. The reasons for choosing a 25-year cut-off are three-fold: first, we had already reported trends and geographic distribution of childhood leukaemia; [27] a second empirical reason was that the time trend curves in the age groups below age 25 and above age 24 had a similar shape (see Supplemental Figure 1); and, third, because the small numbers of cases in each 10-year age group between age 15 and 64 prevented a reliable analysis. We estimated the annual population over the whole region and by administrative unit by extending the 1971, 1981, 1991, and 2001 population census data five years backward and four years onwards. Due to the small number of annual events, we analyzed in more detail trends by sex and specific age groups by interpolation between census years and averaging rates every two consecutive years. We superimposed low-order splines to the plots and used the Joinpoint software, developed by the Statistical Methodology and Applications Branch of the U.S. National Cancer Institute, freely available online, [32] to estimate the annual per cent change (APC) of the ALL standardized rate and detect knots suggestive of change in the slope. We also compared the ALL slopes before and after these knots and by age using the analysis of covariance.

The geographical distribution of the probability of incident cases of childhood and adulthood ALL over the 356 Sardinian communes was explored using a Bayesian approach [33] and plotted on the map of their territorial borders. Such maps are made publicly available by the Italian Institute for Statistics (ISTAT) (https://www.istat.it/it/archivio/104317) under the Creative Commons BY 3.0 IT License.

We previously described in detail the calculation of the posterior probabilities by commune. [27] We first defined the threshold corresponding to $p = 0.001$ in the area of the distribution of the posterior probabilities of ALL incidence around the expectation based on the prior regional rate. We subsequently calculated the likelihood ratio as the ratio between the probability associated with H1 (alternative hypothesis) *vs* H0 (the null hypothesis of chance variation). Finally, we displayed it on the regional map using a chromatic scale of increasing darkness proportional to the probability associated with the alternative hypothesis. We set maps for the total population, by sex and age, whether below or equal to age 24 or above or equal to age 25. We could not explore in more detail the geographical distribution of ALL cases by age range because of their small number above age 15. The analysis was conducted with Bespoke Python code.

We also ranked the 356 communes by the likelihood ratio of ALL incidence before or from age 25 onwards and used Spearman's correlation analysis to explore the spatial correlation between ALL incidence rates in the two age groups.

The available information on possible environmental determinants of ALL included the following: 1) the Italian Institute of Statistics (ISTAT) material deprivation index (http://istat.it) (categories as defined by ISTAT with the less deprived communes as the reference). 2) The distance from the nearest hospital, calculated through the shortest route on the road map (https://maps.google.co.uk), as an indicator of ease of access and, therefore, better chances of a correct diagnosis (rounded quartiles, with the closest as the reference). 3) The natural background radiation as quintiles of the probability of indoor α-emission from radon daughters above the threshold of 300 Bq/m^3 ($\leq$ 5%, 6–10%, 11–20%, 21–30%, 31% or more, as defined by the Regional Agency for Environmental Protection). [34] 4) The geological conformation of the

local territory (quaternary or subsequent marine deposits, basalt and other effusive volcanic rocks, granite and intrusive volcanic rocks, and metamorphic rocks) [35] as an additional indicator of the natural background radiation). 5) The urban/rural type of commune defined based on the presence/absence of the number of administrative, educational, social, judicial, and religious community services being referral for commuters from the surroundings as previously described [36] (empirically categorized in 0, 1–5, 6 or more, with rural communes [0 community services] as the reference). 6) The proximity to large industrial or military areas as modified from Biggeri et al. [37] (binary). And 7) the *per capita* size of livestock (cattle, sheep, and goat farms) in each commune [38] (approximate quartiles, with the lowest as the reference) to explore the hypothesis of a link with potential exposure to zoonotic agents.

We calculated the relative risk for childhood and adult ALL and its 95% confidence interval associated with increasing categories of economic deprivation, distance from the nearest hospital, type of residence (urban *vs* rural), geological conformation, background radiation, proximity to major industrial and military settlements, and per-capita size of livestock, using multivariable Poisson regression analysis and the lowest category, the null category, or the quaternary marine deposits, in the case of the geological conformation, as the reference covariates in the regression model included age, and sex (when exploring type of residence and distance from the nearest hospital) plus type of residence when exploring the rest of the risk factors. The analysis was conducted using SPSS® version 20.0. We conducted sensitivity analyses to further inquire into the positive associations.

The Ethics Committee of the University Hospital of Cagliari approved the use of the 1974–2003 database of incident haemolymphatic malignancies among the Sardinian population for scientific purposes (protocol N. PG 2019/18070, 18 December 2019), in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The authors could only access data in the aggregate form, which made subjects unidentifiable.

3. Results

The median age at diagnosis of the ALL cases was 16.0 years (interquartile range [IQR] 6–45) with a bimodal distribution and a higher prevalence in the pediatric age in both sexes (Fig. 1), consistent with the expectation. The ALL age- and sex-standardized incidence rate (sir) (standard: world population) was 2.0/100,000 (95% CI 1.8 – 2.1) (Table 1), and it was highest at age 0–4 (sir =4.0; 95% CI 3.6 – 4.4) and lowest at age 25–64 (sir = 0.8; 95% CI 0.7 – 0.9). Male cases prevailed at all ages, with the male-to-female cases ratio ranging from 1.12:1 at age 35–44 to 2.45:1 at age 15–24.

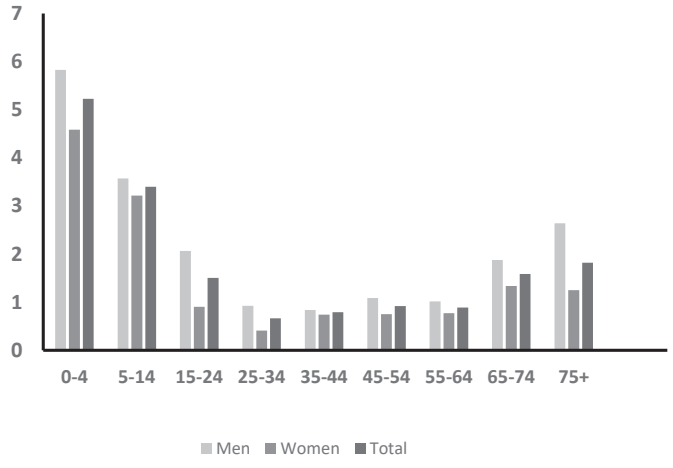

Fig. 1. Incidence of acute lymphoblastic leukaemia by age and sex in Sardinia, Italy.

Table 1
Standardized (World population) incidence rate and Pearson's correlation coefficients describing the time trend of ALL by age group and sex in Sardinia, Italy.

Population subgroup	*No. cases*	*Crude incidence rate x10^{-5}(95% CI)*	*Standardized incidence rate x10^{-5}(95% CI)**
All ages			
men	460	1.9 (1.8 – 2.1)	2.3 (2.1 – 2.4)
women	326	1.3 (1.2 – 1.5)	1.7 (1.5 – 1.8)
total	786	1.5 (1.4 – 1.7)	2.0 (1.8 – 2.1)
0–14 years			
men	209	4.1 (3.6–4.8)	4.4 (3.8–4.9)
women	169	3.6 (3.1–4.1)	3.7 (3.1–4.2)
total	378	3.9 (3.5–4.3)	4.0 (3.6–4.4)
15–24 years			
men	76	1.9 (1.5–2.3)	1.9 (1.5–2.3)
women	31	0.8 (0.5–1.1)	0.8 (0.5–1.1)
total	107	1.3 (1.1–1.6)	1.3 (1.1–1.6)
25–64 years			
men	116	1.0 (0.8–1.1)	1.0 (0.8–1.1)
women	81	0.7 (0.5–0.8)	0.7 (0.5–0.8)
total	197	0.8 (0.7–0.9)	0.8 (0.7–0.9)
65+ years			
men	175	2.2 (1.6–2.7)	2.1 (1.5–2.6)
women	126	1.3 (0.9–1.7)	1.3 (0.9–1.7)
total	301	1.7 (1.4–2.0)	1.7 (1.3–2.0)

Note: *. World Standard population.

3.1. Time trend in ALL incidence

Fig. 2 shows the time trends of ALL in the total population and by sex. For the total population, the annual per cent change (APC) over the study period was −1.4% (95% CI −3.34 - −0.59) and the best fit included a knot separating the downward slope in 1974–1996 (APC = −2.88%, 95% CI −15.69 – 22.34) from the upward trend in 1996–2003 (APC = 11.98%, 95% CI −0.32 – 61.87). However, both trends were non-significant, suggesting chance fluctuations over the study period. Among men, there was no substantial change in ALL incidence over the study period (APC = −2.57%, 95% CI −5.45 – 0.26) and, among women, we observed the same pattern as for the total population with a knot in 1993 and no significant trends before or after 1993 (APC 1974–93 = −6.20%, 95% CI −27.38 – 1.87; APC 1993–2003 = 18.52%, 95% CI −0.32 – 61.87).

After smoothing the population data between the census years and combining the number of events in each two subsequent years along the study period, ALL incidence showed different trend patterns by age (Fig. 3). For the age 0–24 years, there was a sharp decrease in the first 11 years, followed by an increase in the subsequent years, described by a cubic spline with a knot in 1984. As previously noted (Table 1), the majority of cases aged 0–24 years occurred in the pediatric age (0–14 years). However, we could not rule out chance as the explanation for the difference between the ALL slopes before and after 1984 ($p = 0.064$). The same pattern but with a reversed trend direction was observed among the ≥ 65- years age group; we observed significantly opposite slopes with a knot also centred in 1984 ($p = 0.013$). However, the 1974–1984 and 1985–2003 opposite slopes in ALL incidence at ages ≤ 24 and ≥ 25 years were not significantly different ($p = 0.248$ and $p = 0.434$, respectively). The incidence in the 25–64-year age group was lower and represented by a flat line along the study period.

3.2. Spatial distribution of leukaemia

The maps for the total population show that, among men, only one commune had a posterior probability of ALL incidence above the threshold to reject the null hypothesis; among women, there was a cluster of dark spots in the southwestern area (Fig. 4). As explained in

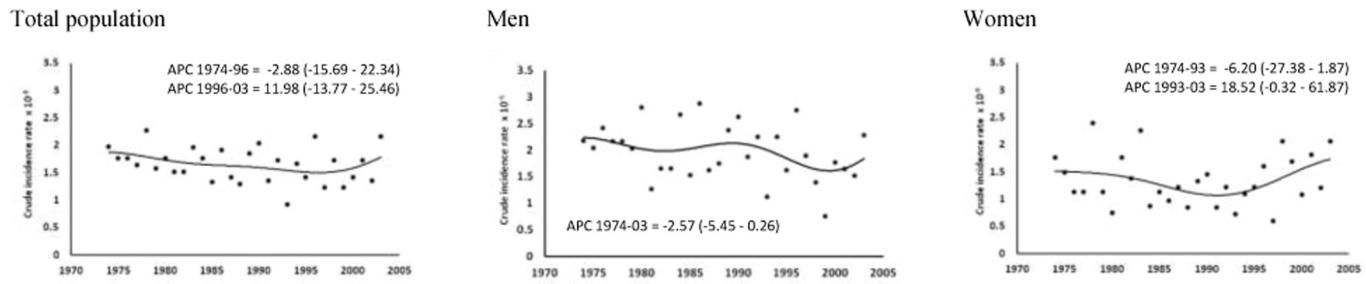

Fig. 2. 1974–2003 incidence rate of acute lymphoblastic leukaemia in the total population of Sardinia, Italy and by sex.

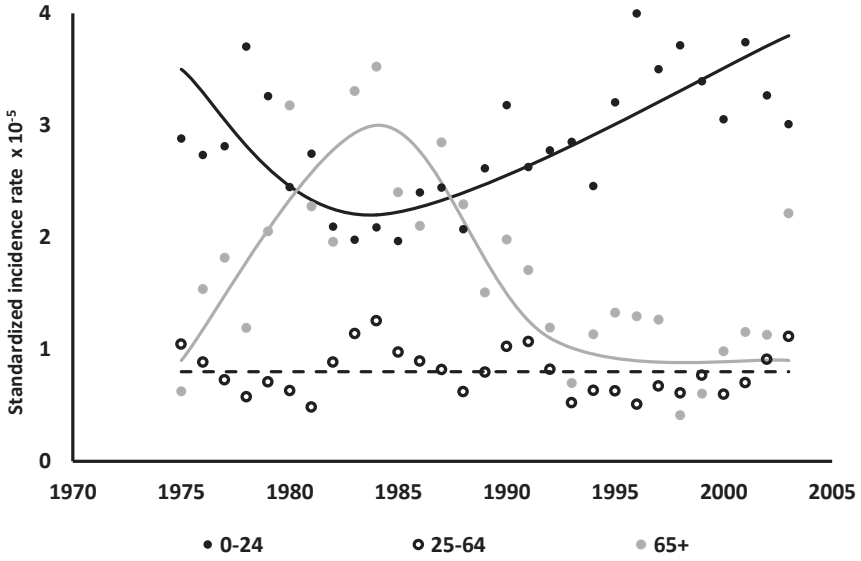

Fig. 3. 1974–2003 incidence rate of acute lymphoblastic leukaemia in the total population of Sardinia, Italy by age group at diagnosis (0–24, 25–64, and 65+-year old).

the Methods section, we also created two maps of the posterior probability of ALL incidence: one for ALL cases diagnosed at age 0–24 and another for those aged 25 or older. Fig. 5 compares these two maps. The visual inspection suggests that ALL at age ≤ 24 clustered in three communes far from each other. The chance of ALL occurrence at age ≥ 25 years was above the threshold only in the major urban centre and region's capital without evidence of spatial aggregation. Across the 356 Sardinian communes, the posterior ALL probabilities at age ≤24 and ≥25 years were not reciprocally correlated (Spearman's correlation coefficient = 0.092, $p = 0.082$, $df = 354$).

3.3. Environmental exposures and socio-economic factors

We investigated environmental variables and economic and social deprivation as determinants of the geographic variation in incidence of ALL separately among children/young adults and adults (Table 2). Risk was elevated among urban residents, about 10% (95% CI <1–22%) below age 25 and 13% (95% CI <1–28%) above or equal to age 25. However, after conducting a sensitivity analysis by excluding the largest urban area, the risk associated with urban residence at age ≤ 24 years did not change, whilst it was null (RR = 1.0, 95% CI 0.82 – 1.12) for the age group ≥25 years. Distance from the nearest hospital, socio-economic deprivation, geology of the residential area, probability of indoor radon levels > 300 Bq/m^3, and livestock density did not affect risk. A modest decrease in risk was observed among residents in communes with a high density of goat breeding at ages ≥ 25 but not ≤ 24 years. Also, the ALL risk was elevated for living in proximity to industrial (RR 1.39, 95% CU 1.07–1.79) and military settlements and shooting ranges (OR = 1.77, 95% CI 1.33–2.36) among the population aged ≥ 25 years but not for those aged ≤ 24 years. However, a sensitivity analysis excluding the most populated urban centre cancelled both associations (RR = 1.14, 95% CI 0.85 – 1.53 and RR = 0.87, 95% CI 0.41 – 1.85, respectively).

4. Discussion

4.1. Time trend in incidence

Our results show that among the population of the regional island of Sardinia, the ALL incidence was substantially stable over the 30-year monitoring period. However, the time trends differed by age, with a sharp downward trend in 1974–1984 followed by an increasing trend in the following years among subjects aged ≤ 24, trends of opposite direction among subjects ≥ 65 years, and just chance fluctuations around a flat trend among subjects aged 25–64 years. We do not have clues to explain such a complex temporal pattern. If not due to chance, different aetiologies shall be suspected for childhood and young adult ALL *vs.* adults and elderly. As it concerns the 1984 peak in ALL incidence followed by a sharp decrease among subjects aged 65+ years, regulatory legislation of benzene, a leukaemogen of widespread domestic use, might have contributed. Regulatory actions initiated in 1971 with the International Labour Office Convention No. 136 [39] and Recommendation No. 144 on the protection against risk of benzene intoxication entered into force on 27 July 1973, which the Italian Law received in 1981. [40] Whether these regulations might have contributed to reducing the ALL incidence among the Sardinian population aged 65+ years from 1985 onwards, is a matter of speculation. Another plausible

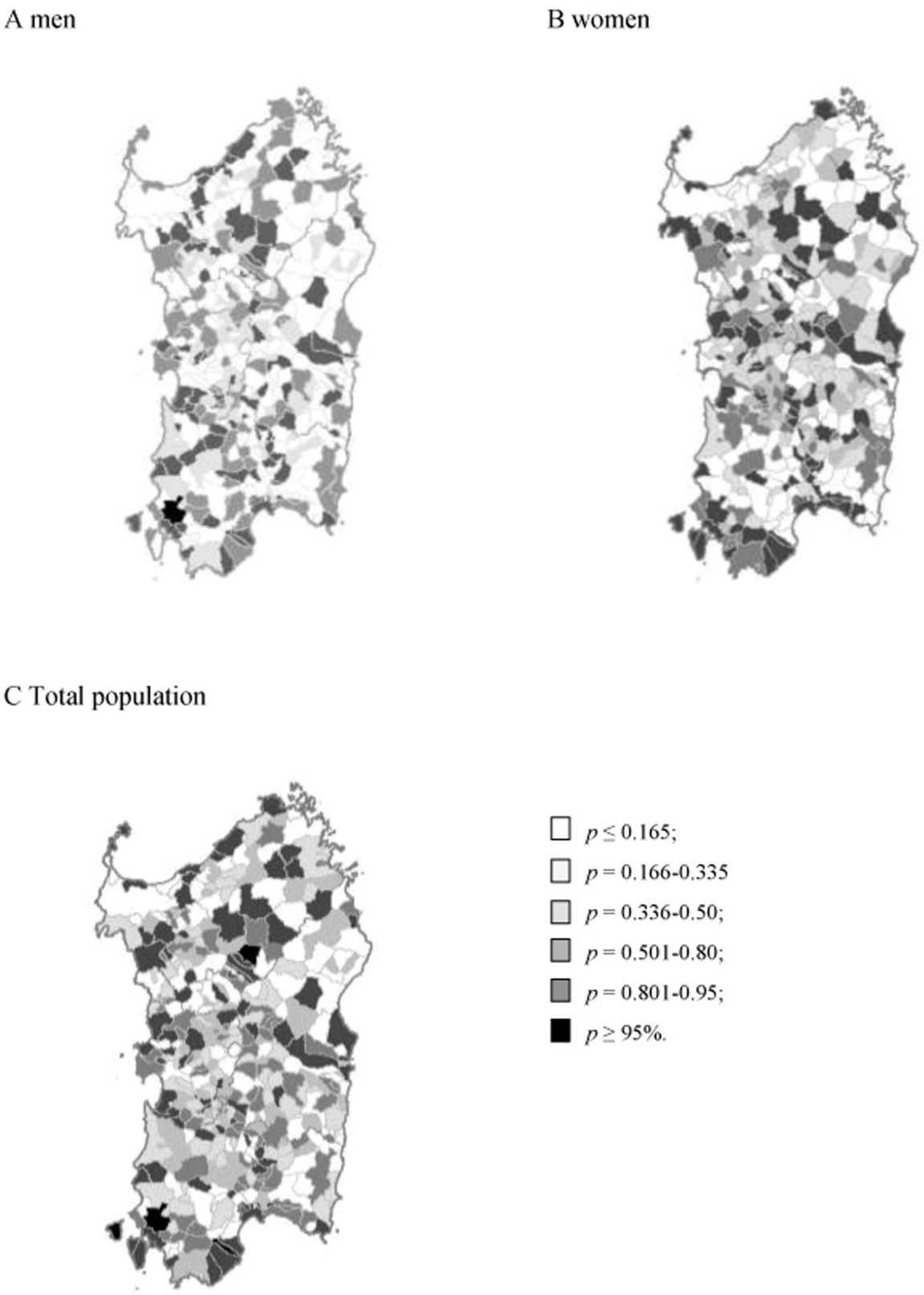

Fig. 4. Map of 1974–2003 incidence of acute lymphoblastic leukaemia in the total population by sex in Sardinia, Italy. The maps of the territorial borders at the commune level are available online from the Italian Institute for Statistics (ISTAT) under the Creative Commons BY 3.0 IT license (https://www.istat.it/it/ archivio/104317).

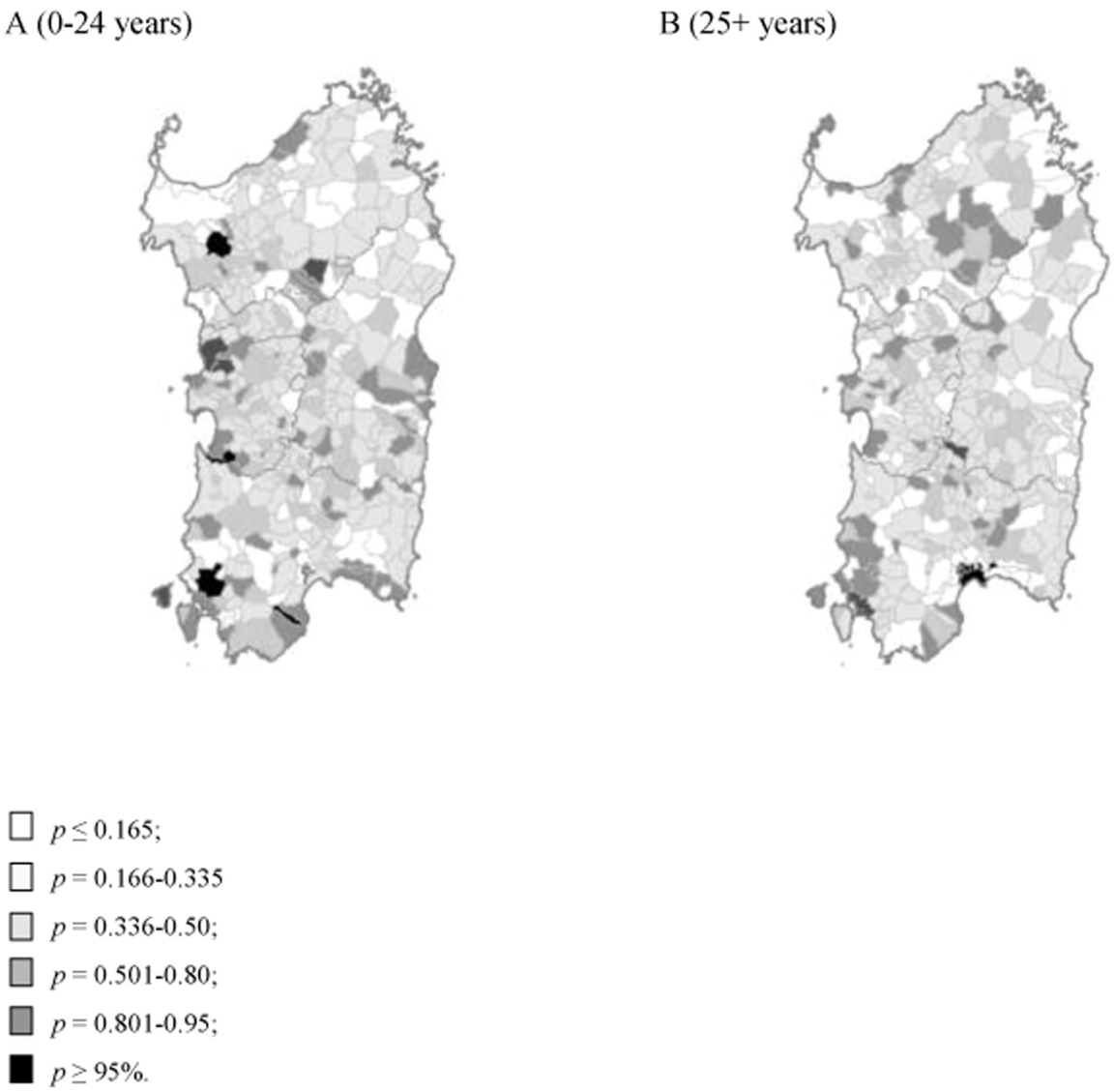

Fig. 5. Map of 1974–2003 incidence of acute lymphoblastic leukaemia in children (age 0–24) (A), adults (age 25+) (B) in Sardinia, Italy. The maps of the territorial borders at the commune level are available online from the Italian Institute for Statistics (ISTAT) under the Creative Commons BY 3.0 IT license (https://www.istat.it/it/archivio/104317).

reason might be the progressive reduction of doses used in diagnostic radiological procedures from the 1960 s [41] A similar study, conducted with the 1943–2003 Danish Cancer Registry data among the population aged 18 years or older, observed a moderate increase [25]. We could not conduct a seasonal analysis as the records in the dataset we used included the year but not the exact date of diagnosis. We could not retrieve published reports describing long-term trends in the ALL incidence among adults. Our analysis suggests changes in ALL incidence around specific knots in time, but we could not find evidence of periodical oscillations overall and by age group.

4.2. Spatial distribution of leukaemia

Several studies reported an unequal geographic distribution of leukaemia cases. For instance, the incidence of acute lymphatic leukaemia was much lower in an island in the east of Shanghai compared to the other districts covered by the Shanghai Cancer Registry. [26] We observed a hot spot in a southwestern commune among men and a cluster of increased probabilities among women in the same southwestern area. Our study was the first to address the geographical distribution of ALL cases by age and gender in Sardinia and the first report about and excess of adult ALL cases among the female population in that southwestern area. One of these communes, the one where the probability of an elevated ALL incidence among men and women was the highest, was the site of a robust cluster of childhood leukaemia in the 1980 s [42] From the early 1970 s up to recently, the area was the site of the largest industrial settlement in the region, with a lead and zinc smelting plant, a primary aluminium foundry, and a large coal-fired power plant. In the past century, it was the main coal mining area in Italy. The childhood ALL cluster disappeared in the 1990 s, and there was no evidence of a link with industrial emissions. [43] Whether the local industrial history might explain the ALL clustering among women residing in the area is unknown. Among the adult population, only the largest commune in the area had a posterior probability of ALL incidence above the threshold we set to reject the null hypothesis ($p < 0.001$), which accounted for the excess risk associated with urban residence. Over the 356 Sardinian communes, the posterior probabilities of ALL incidence at age ≥25 years did not match those below that age, suggesting differences in the etiologic pattern, histology, or both.

Table 2
Risk of acute lymphoblastic leukaemia in the Sardinian population aged ≤24 or ≥ 25+ years by environmental risk factors. Fifteen ALL cases with unknown residence (nine aged ≤24 and six aged ≥ 25 ALL cases) were excluded from the analysis.

	Age ≤ 24 years		Age ≥ 25 years	
Environmental factors	Person-years	Cases RR 95% CI	Person-years	Cases RR 95% CI
Type of residence				
Rural	7629,482	182 1.00 reference	13,383,192	121 1.00 reference
Small towns	3265,636	97 1.37 0.78–2.38	5439,614	44 0.92 0.65–1.30
Urban	6823,922	197 1.11 1.00–1.22	11,885,024	130 1.13 1.00–1.28
Distance from nearest hospital				
≤ 13 km	10,363,570	278 1.00 reference	17,823,908	175 1.00 reference
14–21 km	3225,158	80 0.92 0.72–1.18	5540,020	58 1.03 0.76–1.38
22–29 km	2292,642	68 1.05 0.92–1.20	4080,322	36 0.92 0.77–1.10
≥ 30 km	1837,670	50 1.00 0.91–1.11	3263,580	26 0.91 0.80–1.05
Deprivation index				
1st quintile	2947,862	106 1.00 reference	5056,256	39 1.00 reference
2nd quintile	4201,714	117 0.81 0.62–1.05	7531,064	99 1.70 1.17–2.46
3rd quintile	3650,698	77 0.77 0.66–0.89	6228,898	53 1.05 0.85–1.29
4th quintile	3573,704	86 0.88 0.80–0.97	6295,948	52 1.02 0.89–1.17
5th quintile	3345,062	90 0.93 0.87–1.00	5595,664	52 1.04 0.94–1.15
Geological features				
Quaternary or subsequent marine deposits	12,121,106	340 1.00 reference	20,431,360	210 1.00 reference
Basalt and other effusive volcanic rocks	1621,506	38 0.91 0.64–1.28	3041,756	24 0.77 0.50–1.19
Granite and intrusive volcanic rocks	1763,622	45 0.98 0.84–1.15	3077,080	26 0.93 0.75–1.14
Metamorphic rocks	2312,806	53 0.94 0.86–1.04	4157,634	35 0.93 0.83–1.05
Probability of indoor radon > 300 Bq/m^3				
< 5%	3469,400	114 1.00 reference	6256,662	101 1.00 reference
5 – 9.9%	4938,606	134 0.85 0.64–1.12	8369,782	70 0.51 0.37–0.82
10 – 19.9%	5495,658	144 0.87 0.75–1.00	9393,650	71 0.69 0.57–0.82
20 – 29.9%	2431,232	53 0.87 0.77–0.98	4156,986	30 0.77 0.66–0.89
≥ 30%	1384,144	31 0.92 0.82–1.04	2530,750	23 0.85 0.75–0.98
	Age ≤ 24 years		Age ≥ 25 years	
Environmental factors	Person-years	Cases RR 95% CI	Person-years	Cases RR 95% CI
Cattle per resident				
None	12,000,206	337 1.00 reference	20,666,688	226 1.00 reference
0.03 – 0.10	3373,722	76 0.72 0.56–0.94	5904,878	37 0.49 0.34–0.71
> 0.11	2345,112	63 1.01 0.88–1.16	4136,264	32 0.86 0.71–1.04
Sheep per resident				
< 1.43	11,035,398	310 1.00 reference	18,777,890	204 1.00 reference
1.43 – 3.349	3422,308	90 1.04 0.79–1.37	5795,602	41 0.60 0.42–0.88
≥ 3.35	3261,434	76 0.96 0.83–1.12	6134,338	50 0.84 0.70–1.01
Goats per resident				
< 1.43	4649,918	127 1.00 reference	8179,278	111 1.00 reference
1.43 – 3.349	6736,080	187 1.07 0.85–1.34	11,446,956	86 0.56 0.42–0.75
3.35 – 6.05	6333,042	162 1.03 0.88–1.20	11,081,596	98 0.82 0.68–0.98
Industries/mines				
No	10,523,550	275 1.00 reference	18,418,290	153 1.00 reference
Yes	7195,490	201 1.01 0.82–1.23	12,289,540	142 1.39 1.07–1.79
Cork harvesting				
No	17,464,634	471 1.00 reference	30,227,426	289 1.00 reference
Yes	254,406	5 0.75 0.31–1.81	480,404	6 1.22 0.54–2.75
Military settlements & shooting ranges				
No	14,851,372	397 1.00 reference	25,529,900	217 1.00 reference
Yes	2867,668	79 0.97 0.75–1.26	5177,93	78 1.77 1.33–2.36

4.3. Environmental exposures and socio-economic factors

We explored several environmental exposures as possible determinants of the geographic variation of ALL by sex and age. A link between environmental exposure to chemical fertilizers and acute leukaemia emerged in Dagestan, Russia; [44] mortality from haemolymphatic malignancies showed a correlation with agricultural pesticide use in 34 drainage basins in Quebec in 1976–1985, [45] and arsenic contamination of groundwater was suggested as a determinant of leukaemia cases (all forms) in the Gange plain, India. [46] In New Jersey, U.S.A., the standardized incidence ratio of leukaemia (all forms) in the towns was elevated in the highest tertile of volatile organic compounds (VOC) contamination in the drinking water, based on Poisson regression analysis. [47] Also, a 9.5% annual increase in leukaemia incidence (all forms) occurred among women in the Taean County of Korea following an oil spillage in 2007, compared with a 0.6% annual per cent change over the whole country in the same period. [48] Based on the Third National Cancer Survey using U.S. SEER data, ALL incidence in men showed a correlation with cattle, especially dairy cattle density. [49] Interestingly, counties where dairy herds affected with bovine lymphosarcoma prevailed showed an excess ALL incidence. The natural background radiation and, specifically, the α and γ radiation levels in the ground depend on the geology of a territory. [50] A high background radiation was associated with an increase of chromosomal aberrations among the resident population in China, [51] and low-level ionizing radiation from various sources, including four studies about the natural background radioactivity, was associated with an excess risk of overall leukaemia in a review. [52] Geological features, but not radon levels and gamma radiation, were associated with myeloid leukaemia in an Italian study. [53] On the other hand, ^{222}Rn activity above 90 Bq/m^3 was well correlated with an increase in leukaemia incidence in a study covering selected areas of Russia, China, and France. [54] In this paper, we explored two surrogates of the natural background radiation, namely the geology and the probability of an environmental indoor α-radiation level >300 Bq/m^3, as possibly related to the geographic spread of ALL. We did not find evidence of an association with the geology and observed a significant decrease in risk with the probability of indoor exposure to radon among adults. However, there was no trend with increasing probability of exposure and, therefore, while not excluding hormetic effects of low-level α-radiation, we interpret such finding as

due to chance.

Urban residence posed a significant, though marginal, risk for ALL at age ≤24. As for livestock, the risk of adult ALL decreased with the prevalence of goat-breeding, with a significant inverse trend (Wald test for trend: $p = 0.008$). We are unaware of previous studies suggesting such an association; therefore, we interpret it as a chance finding. As it concerns residential risk factors, residence near industrial or military settlements was associated with the risk of adult ALL. However, sensitivity analyses excluding the largest urban area in the region showed no excess. Also, ALL risk at age above or equal to 25 years was null for urban residents following the same sensitivity analysis. These results suggest that other urban factors, such as environmental exposure to benzene from vehicular traffic, might be plausible explanations for the observed associations. Previous studies comparing environmental benzene levels around industrial settlements and in the same urban area mentioned in this paper would support this alternative explanation. [55] A further alternative explanation might be the lack of protective factors associated with rural residence, such as early contact with infectious agents.

5. Limitations

The use of an old database limits its use for Public Health and Prevention purposes. Still, this unique database made it possible to detect previously unexplored age-related changes in the time trend, geographic spread, and epidemiological associations of ALL.

Pathological specimens and clinical and bio-molecular information were unavailable to explore the ALL epidemiology by subtype. Therefore, we cannot tell whether the observed associations and the differences between childhood and adult ALL might have been due to the varying prevalence of the distinct ALL subtypes and/or different etiological agents.

The expertise of the local physician/s in detecting the disease and the proximity to an oncohaematology unit would plausibly explain the observed association with urban residence and the excess cases in the largest urban area. In the case of a linear upward trend, such expertise might have increased along the study period due to increased reporting (detection bias). However, the varying ALL slopes by age would exclude that such bias affected our results. Post-diagnosis relocation of the families seems unlikely to have occurred, as, among the population aged ≤ 24 years, smaller communes lacking hospitals with specialist oncohaematology units matched the excess ALL cases observed in the largest urban area in the region. The information on the commune of residence at the time of diagnosis was missing for 15/786 patients (2.0%), equally distributed between children (9/485, 1.9%) and adults (6/301, 2.0%); it seems reasonable to exclude that this might have affected the geographic patterns.

We defined residence at the time of diagnosis, which might have implied misclassification of past exposures among adult cases. We acknowledge this as a limitation in interpreting our results.

While we would not deny the explorative value of ecological studies, [56] we acknowledge the possibility of bias due to the “ecological fallacy”. Therefore, with due caution, we stress the scientific relevance of our findings and recommend further studies to support or reject them.

Author statement

Prof. Giorgio Broccia initiated the data base and continued it along his career as Director of the Hematology Department of the Cagliari Oncology Hospital up to retirement. He also contributed in reviewing all the diagnoses, and in writing and revising the manuscript. Dr Jonathan Carter conducted the Bayesian analysis of the probability of incident acute lymphocytic leukemia by administrative unit over the whole territory of the region of Sardinia. Cansu Ozsin-Ozler cured the graphics and revised the manuscript. Sara De Matteis contributed to the analysis and revised the manuscript. Pierluigi Cocco designed the study, supervised its development, drafted the manuscript, revised it, and assumed the role of corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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