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ARTICLE

Epidemiology of Chronic Lymphocytic Leukemia in Sardinia, Italy (1974–2003)

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Several reports have described a worldwide increasing incidence of chronic lymphocytic leukemia (CLL) dating back seven to eight decades. Although genetic susceptibility would be an implausible explanation, the determinants of this upward trend and its spatial coordinates are poorly understood. We explored CLL incidence in Sardinia, Italy, using a validated database including the 1700 CLL cases diagnosed during 1974–2003. We applied Bayesian methods to map the CLL probability by administrative unit and Poisson regression analysis to investigate socioeconomic and environmental determinants adjusting by possible confounders. The standardized (Standard European population) incidence rate for the Sardinian population over the study period was 5.1 per 100,000 (95% confidence interval [CI] 4.9–5.3), increased annually by 5.8% (95% CI 5.7–6.0) consistently by sex and age, and was more noticeable in urban areas. Five administrative units exceeded the 95% posterior probability of an elevated CLL incidence: these were rural areas spread over the regional territory, not suggestive of spatial clustering. The Poisson regression analysis showed that the risk was elevated in urban areas (RR = 1.11, 95% CI 1.05–1.17), among residents $\geq$ 30 km from the nearest hospital (RR = 1.09, 95% CI 1.06–1.12), and with the local prevalence of cork harvesting (RR = 1.62, 95% CI 1.12–2.34). Our results suggest that better access to health care facilities and improvements in diagnostic efficacy might have generated the observed upward trend in CLL incidence, along with contributing environmental factors.

HIGHLIGHTS

- In Sardinia, Italy, chronic lymphocytic leukemia (CLL) incidence increased 5.5%/year during 1974–2003.
- CLL risk was elevated in five sparse communes and urban areas.
- Risk increased with distance from hospitals and cork harvesting.

Chronic lymphocytic leukemia (CLL) is a multifaceted, multifactorial disease caused by the monoclonal expansion of B lymphocytes, which become unresponsive to physiological blocks of replication and accumulate in the peripheral blood, bone marrow, and secondary lymphoid organ [1]. This lymphoid malignancy typically affects elderly men, with an average age at diagnosis approximately 70 years and less than 15% of cases arising at age 60 years or earlier [2]. Monoclonal CLL lymphocytes exhibit a peculiar immunophenotype CD19-, CD23-, and CD5-positive, and low expression of CD20 and surface immunoglobulins [3]. Most CLL cases are indolent, do not require treatment, or respond well to therapy when necessary. However, cases featuring chromosome 17 deletion or p53 mutations are clinically aggressive, resistant to therapy, and have a less-favorable prognosis [4]. A variety of genetic and environmental factors influence CLL etiology. Based on GWAS studies, heritable factors would account for 16.4% (95% confidence interval [CI] 10.5–22.2%) of the incident cases [5], and the attributable fraction due to known occupational exposures, such as pesticides, solvents, sterilizing agents, and contact with raw meat would be 12.1% (95% CI 3.6–19.2%) [6]. Multiple conditions, including pre-existing diseases, therapeutic agents, and infectious agents, have also been proposed [7], but the etiology of most CLL cases remains unclear.

CLL is considered to be a mature B-cell lymphoma [8]. However, for purposes of historic and geographic comparisons, Cancer Registries worldwide continue to register it separately from the rest of the non-Hodgkin lymphomas (NHLs) but, in most instances, incorporate the acute and chronic forms of lymphocytic leukemia into the single category of lymphoid leukemia, despite presenting different epidemiologic features and possibly a different etiology. A few reports, overcoming the classification difficulties, described its epidemiologic features.

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In 2004−2009, the annual age-adjusted rate of CLL in the United Kingdom was 5.0 (4.8−5.1) × 100,000 [9], whereas it was 1.2 × 100,000 in the total Chilean population and 0.09 × 100,000 in the native Amerindian population in 2012−2019 [10]. In Denmark, age-standardized incidence rates increased in both sexes from 1943 to 2003 [11]. A similar increase was observed in Taiwan from 0.36 to 0.54 × 100,000 in 2006−2015, although the incidence rate was lower than that in populations of European descent [12]. CLL is rare among Asians. However, among the Chinese, cases appear at younger ages and with more aggressive clinical behavior [13]. Interestingly, consistent with a genetic component, the lower propensity to develop CLL persists among the Chinese migrant population [14].

The geographic variation in CLL incidence has been poorly investigated. CLL incidence did not show a geographic pattern in the northern and central regions of Italy [15], whereas, in 478 US counties, the incidence showed a correlation with residential radon exposure [16].

In this study, we used the 1974−2003 database of incident hematologic malignancies in Sardinia, a region of Italy and the second largest Island in the Mediterranean Sea, to explore the time trend and geographic distribution of CLL ICD-10 code C91.1), as well as its relationship with ecologic and lifestyle variables.

MATERIAL AND METHODS

Study Population

The database of all hematologic malignancies diagnosed in the Sardinian population in 1974−2003 was previously described [17] and validated [18]. Briefly, all incident cases of hematologic malignancy diagnosed among Sardinian residents in 1974−1993 were identified with an active survey through the registries of the clinical and pathologic institutions operating over the entire region during that time. The senior hematologist who promoted the initiative (G.B.) personally reviewed each diagnosis by accessing the patients' clinical records and discussing them with the attending hematologist and/or medical staff. Data for this report were made available in the form of anonymous records grouped by sex as assigned at birth, 10-year age groups, residence, diagnosis, and year of diagnosis. Within a total of 14,452 records, we extracted 1700 cases of CLL, including 671 female and 1029 male cases. Residence at the time of diagnosis was missing for 52 cases (3.0%); we included these in calculating the prior age- and sex-specific regional rates and in the analysis of the time trend but not in the risk maps by residential units nor in the exploration of environmental risk factors.

Statistical Methods

For each of the 356 Sardinian communes, as the autonomous administrative units are defined in Italy, existing in 1974, we calculated the CLL standardized annual incidence rate during the study period by applying the 1974−2003 regional rates to person-years in the corresponding age and sex strata of the local population. Another 21 autonomous communes were established in the subsequent years, which we kept incorporated with those of origin to preserve the consistency of the initial map across the years. The structure of the Sardinian population changed during the study period, as reflected by the three population censuses that took place in 1971, 1981, 1991, and 2001, with progressive aging due to the reduction in the size of the younger and the increase of the older age classes. For each of the 356 communes, we estimated the annual number of residents in each age- and sex stratum for every year in the study period by extending the corresponding census population four years backward and five years onwards. The person-years in each age- and sex stratum was the sum of the annual residents over the 30-year study period. The expected events resulted from applying the age- and sex-specific regional rates to the person-years in the corresponding strata of each commune. This procedure allowed us to account for the changing structure of the local and regional population. For comparison with international statistics, we also calculated the annual standardized incidence rate of the regional population using the 2011−2030 European Standard population (https://www.opendata.nhs.scot/dataset/standard-populations/resource/ 29ce4cda-a831-40f4-af24-636196e05c1a) and the World standard population, as recommended by the Cancer Incidence in the Five Continents volumes periodically issued by the International Agency for Research on Cancer (IARC-CI5C) [19]. We used univariate regression analysis and the average annual percent change (APC) and its 95% confidence interval to calculate the time trend in 1974−2003. Based on the R^2 value associated with different regression equations, we assumed a linear relationship and tested the null hypothesis of no time variation using the Pearson correlation coefficient. The null hypothesis was rejected if associated with a probability < 0.05.

The variation in the probability of CLL occurrence over the regional territory, subdivided into the areas of the 356 communes, was calculated using a Bayesian approach [20]. We used maps of the Italian Institute for Statistics (ISTAT) (https://www.istat.it/it/archivio/104317) publicly available under the Creative Commons BY 3.0 IT License. The calculation of the posterior probabilities by communes has been previously described in detail [18]. The analysis was conducted with Bespoke Python code.

Based on the distribution of the likelihood ratio, that is the ratio between the H_1 probability of exceeding the prior incidence rate and the H_0 probability of chance variation, we used the following chromatic scale for the area of each commune: white $p \leq 0.165$, light gray $p = 0.166\text{-}0.335$, medium-light gray $p = 0.336\text{-}0.50$, medium-dark gray $p = 0.501-0.80$, dark gray $p = 0.801-0.95$. A few communes with a probability higher than 95% had a black shade.

Potential CLL risk factors were investigated using Poisson regression models adjusted for the following commune-specific covariates: 1) the proportion of residents aged 75 years or more (the oldest age group for which aggregated data were made available), 2) deprivation index (http://istat.it), and 3) distance from the nearest hospital based on the shortest route. The following risk factors were also considered: 1. the background natural radiation in quintiles of the probability of α-emission from radon daughters above 300 Bq/m^3 ($\leq$5%, 6%−10%, 11%−20%, 21%−30%, 31% or more), the threshold level indicated in the EURATOM directive 59/2013/Euratom, as the annual average of the indoor radon concentration [21]; 2. the geology of the local territory (quaternary or subsequent marine deposits, basalt and other effusive volcanic rocks, granite and intrusive volcanic rocks, and metamorphic rocks) [22]; 3. the urban or rural type of commune, as defined by five community services (administrative, educational, health, judicial, and religious) attracting daily commuters from the surroundings; 4. presence of potential sources of pollution, including large industrial or military settlements, mines or quarries, and cork farms, in the surroundings, as modified from Biggeri et al. [23]; 5. the livestock size (cattle, sheep, and goat farms) [24] relative to the local residents, as a potential source of exposure to zoonotic agents.

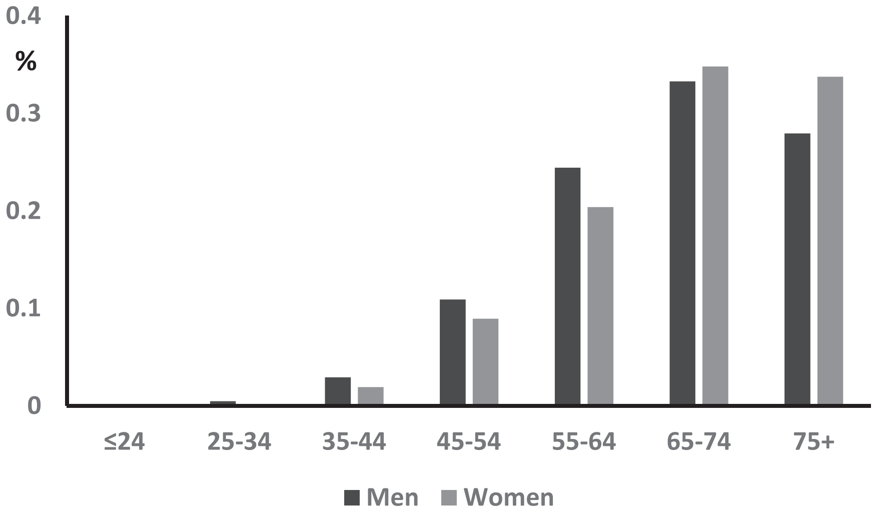

Figure 1 Age distribution of the prevalence of chronic lymphocytic leukemia, by age and sex.

The relative risk and its 95% confidence interval associated with increasing categories of economic deprivation, distance from the nearest hospital, type of residence (urban or rural), geology, background radiation, proximity to potential sources of environmental pollution, and per-capita livestock size, were calculated with the lowest category, the null category, or the quaternary marine deposits in the case of geology, as the reference. The analysis was conducted using SPSS version 20.0.

The Ethics Committee of the University Hospital of Cagliari approved the use of the 1974−2003 database of incident hematologic malignancies in Sardinia for scientific purposes, in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki), on December 18, 2019 (protocol No. PG 2019/18070),

RESULTS

The average age at diagnosis was 67.8 years (SD 11.31); the female cases were slightly older (women: mean age: 69.0 years, SD 11.03; men: mean age: 67.1 years, SD 11.43; $p = 0.043$). The male-to-female ratio was 1.5:1. Figure 1 shows the age distribution of the cases. The youngest patient with CLL case was a 29-year-old man. Another male and one female patient were diagnosed at the age of 30 years. The highest prevalence was in the 70−74 age class, followed by subjects diagnosed at 75 years or older, whose slightly lower prevalence was more accentuated among men.

Time Trend in Incidence

Table 1 shows the age- and sex-adjusted incidence rates with both the European Standard population and the World standard population as the standards. The 1974−2003 CLL incidence in Sardinia was slightly higher than that reported in the United Kingdom in 2004−2009 [9] and in the European Haemacare study in 2000−2002 [26], and lower than that reported in Switzerland in 1997−2016 [26]. The world population age- and sex-standardized incidence rate was 2.3 (95% CI 2.2−2.5).

The graphs in Figure 2 show the trend of CLL over the 30 years of study by sex. Incidence of CLL increased linearly (APC: 5.8%, 95% CI 5.7−6.0) during the study period, similarly in both sexes (men: APC: 5.5%, 95% CI 5.4−5.7; women: 5.8%, 95% CI 5.7−5.9), and

Table 1 Linear regression coefficients describing the time trend of CLL incidence by age group and sex

	Men	Women	Total population
No. of 1974−2003 incident cases of CLL	1027	672	1699
Incidence rate[a] (95% CI)	4.3 (4.0−4.6)	2.6 (2.4−2.8)	3.4 (3.3−3.6)
Standardized incidence rate[b] (95% CI)	3.0 (2.8−3.2)	1.6 (1.5−1.8)	2.3 (2.2−2.5)
Standardized incidence rate[c] (95% CI)	6.7 (6.3−7.0)	3.6 (3.4−3.9)	5.1 (4.9−5.3)
APC %(95% CI)	5.5 (5.4−5.6)	5.8 (5.7−5.9)	5.8 (5.7−6.0)
Pearson correlation coefficient	0.839	0.806	0.877
p value	<0.0001	<0.0001	<0.0001

APC = Annual percent change; *CLL* = chronic lymphocytic leukemia.
a Incidence rate based on the age and sex structure of the Sardinian population in the Italian 1971, 1981, 1991, and 2001 population censuses
b World standard population
c European standard population.

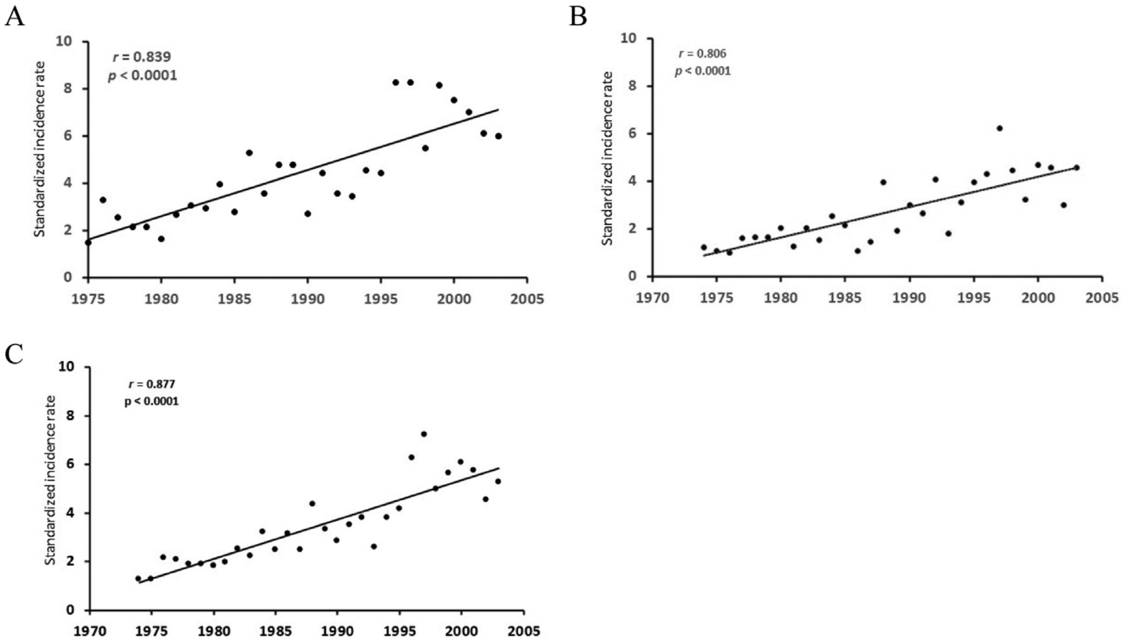

Figure 2 1974−2003 Incidence rate of CLL in the total population **(A)**, and the female **(B)**, and male **(C)** adult population in Sardinia, Italy. CLL = Chronic lymphatic leukemia.

for cases diagnosed between25 and 64 years(APC = 3.2%,95% CI 3.0−3.4)or 65 years or more(APC = 3.8%, 95% CI 3.6−4.0).The APC was more accentuated in urban (APC: 6.6%, 95% CI 6.5−6.7) than rural residents (APC: 4.2%, 95% CI 4.0−4.3). After plotting the residuals versus the predicted values, we did not detect any sudden change in the slope [27].

Spatial Distribution

Figure 3 shows the map of the probability of the CLL incidence rate above the prior critical threshold by commune. Five communes exceededthe95%probability of an elevated posterior incidence of CLL. On visual inspection of the map, these communes appeared sparsely distributed over the Sardinian territory, with no clear evidence of clustering in specific areas. Two are located in the inner mountainous area, two are on the side of a plateau known for horse breeding in the wild (La Giara), and the last is on the northwestern side of the island. Among the residents in these high-risk communes, both sexes shared a high posterior probability of CLL incidence, although it was higher in the male population. Notably, none of these five communes had a high probability of an excess incidence of NHL or multiple myeloma (MM) [18,28].

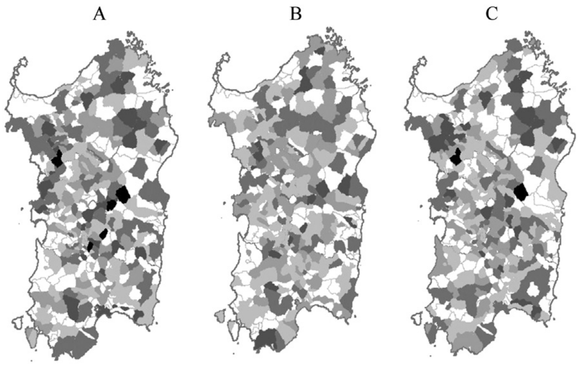

Figure 3 Map of 1974−2003 incidence of chronic lymphatic leukemia in the overall population **(A)**, in the female **(B)**, and male **(C)** population in Sardinia, Italy. The maps of the territorial borders at the commune level are available online from the Italian Institute for Statistics (ISTAT) under the Creative Commons BY 3.0 IT license (https://www.istat.it/it/archivio/104317).

Environmental Exposures and Socioeconomic Factors

Table 2 shows the results of the Poisson regression analysis exploring the association between CLL incidence and environmental and socioeconomic variables. Urban residence with reference to rural communes (RR = 1.11, 95% 1.05−1.17) and residing ≥30 km from the nearest hospital to concerning communes with a hospital (RR = 1.09, 95% CI 1.06−1.12) were significant risk factors. CLL risk did not vary by the deprivation index, geology, increasing probability of elevated indoor radon levels, per-capita cattle, sheep, or goat breeding, or proximity to industrial or military settlements. However, the risk was elevated for in an area with a high prevalence of cork harvesting, although only three communes (one urban and two rural areas) and 37 cases contributed to the exposed category.

DISCUSSION

Time Trend in Incidence

Our results show that from 1974 to 2003, the incidence of CLL increased by 5.8%/year in Sardinia, Italy, consistent with what we previously reported for NHL and MM [18,28]. Our observation of an increasing incidence of CLL reflects what was observed at the global level for the period 1990−2017 [29], in the United Kingdom

Table 2 Risk of chronic lymphocytic leukemia in relation to urbanization of the residence town, distance from the nearest hospital, geological characteristics of the residence area, background radiation, increasing quartile of livestock, and major economic activities in the surroundings

Environmental factors	Person-years	Cases RR 95% CI
Type of residence		
Rural	21,012,674	7391.00 reference
Small towns	8,705,250	2600.99 0.86−1.14
Urban	18,708,946	3271.11 1.05−1.17
Distance from nearest hospital (km)		
≤ 13	28,187,478	9601.00 reference
14−21	8,765,178	2160.90 0.84−0.97
22−29	6,372,964	7970.96 0.92−1.02
≥ 30	5,101,250	7021.09 1.06−1.12
Deprivation index		
Lowest quintile	8,004,118	2671.00 reference
Second quintile	11,732,778	4271.07 0.92−1.25
Third quintile	9,879,596	3170.97 0.89−1.05
Fourth quintile	9,869,652	3350.99 0.94−1.05
Fifth quintile	8,940,726	3020.99 0.95−1.03
Geological features		
Quaternary or subsequent marine deposits	32,452,466	1,0831.00reference
Basalt and other effusive volcanic rocks	4,663,262	1750.69 0.45−1.06
Granite and intrusive volcanic rocks	4,840,702	1570.89 0.80−1.00
Metamorphic rocks	6,470,440	2330.97 0.88−1.06
Probability of indoor radon > 300 Bq/m^3		
<5%	9,726,062	3561.00reference
5−9.9 %	13,308,388	4410.77 0.54−1.10
10−19.9%	14,889,308	5030.92 0.81−1.04
20−29.9%	6,588,218	1931.00 0.91−1.09
≥30%	3,914,894	1551.04 0.98−1.11
Cattle per resident		
None	32,666,894	1,1171.00reference
0.03−0.10	9,278,600	3030.91 0.77−1.07
> 0.11	6,481,376	2281.00 0.93−1.09
Sheep per resident		
<1.43	33,210,636	1,0751.00reference
1.43−3.349	9,217,810	2950.80 0.43−1.47
3.35−6.05	5,826,018	2420.85 0.47−1.53
> 0.65	3,569,754	1410.65 0.37−1.15
Goats per resident		
<1.43	12,829,196	4611.00reference
1.43−3.349	18,183,036	5840.87 0.76−1.00
3.35−6.05	17,414,638	6030.94 0.86−1.02
Industries/mines		
No	28,941,840	9991.00reference
Yes	19,485,030	6491.03 0.91−1.16
Cork harvesting		
No	47,692,060	1,6111.00 reference
Yes	734,810	371.621.12−2.34
Military settlements and shooting ranges		
No	40,381,272	1,3401.00 reference
Yes	8,045,598	3081.080.92−1.27

[9], Denmark in 1943−2003 [11], and Taiwan in 2006−2015 [12] but not in Switzerland from 1997 to 2016 [25]. In the United States, the CLL incidence increased from 1975 to 2000 and remained stable in the subsequent years [30].

Spatial Distribution

Although other lymphoproliferative neoplasms, such as NHL and MM, tended to cluster in the northern part of the region [18,28], we did not find evidence that this was the case also for CLL. A few communes had an increased risk but were unrelated to those with an elevated incidence of NHL or MM. The international variation in CLL incidence is well known. Although it is the most prevalent form of leukemia in Australia, New Zealand, the United States, and Europe [31], low incidence rates have been reported in Chile [10] and Asian populations [32], with genetics more than environmental factors as the proposed determinants. Moreover, Asian CLL cases occur at a younger age than among subjects of European ancestry, with atypical morphologic and immunologic features, a higher prevalence of mutations in the immunoglobulin heavy chain gene (IGHV), and shorter freedom-from-progression intervals [33]. We are unaware of studies that have explored the geographic spread of CLL in small areas within countries.

Environmental Exposures and Socioeconomic Factors

Contrary to the relative abundance of ecologic studies on hemolymphatic cancer or leukemia overall [34−37], the lack of studies on the geographic variation of CLL results in poor knowledge of its environmental determinants. Analytical studies have suggested a link with several occupational exposures, including pesticides [38], solvents [39], and particularly benzene [39], ethylene oxide [40], and ionizing radiation [41,42]. Working on a farm [43], raising livestock [44], contact with meat [45], and working at oil refineries [46] have also been implicated. However, whether such exposures might also explain part of the upward time trend and geographic variation in CLL risk at the population level remains unknown.

Based on publicly available data, we explored the link with socioeconomic conditions and several possible environmental factors, including the degree of urbanization, geologic features, probability of environmental exposure to radon above the threshold of 300 Bq/m^3, and residence in communes with a high prevalence of cattle, sheep, and goat breeding or with industrial or military settlements in the surroundings or with cork harvesting as a relevant feature of the local economy.

Residence in urban areas, or more than 30 km from the nearest hospital, was associated with a significant increase in risk, suggesting that difficulty in accessing health care facilities may have played a role. The CLL incidence did not vary according to the geologic conformation of the territory or the probability of radon levels exceeding 300 Bq/m^3 did not affect the risk. Regarding livestock, an elevated prevalence of cattle breeding in the commune of residence did not match the excess CLL risk among cattle breeders observed in a case−control study [44]. The probability of an increase in CLL incidence was also unrelated to sheep and goat breeding. Residence in cork harvesting centers conveyed an increase in CLL risk. Instead, there was no association with residency in the surroundings of industrial or military settlements.

Advantages and Limitations

A limitation of our study is that the incidence data refer back in time and might not reflect the current situation. However, motives of interest include its extension over three decades in an area where the incidence of specific hematologic malignancies was not previously evaluated and the agreement of our results with those from other European countries recorded within the same time frame. The senior hematologist (G.B.) who initiated the database did so long before the local Cancer Registries began operating and extended his survey to the entire region. Instead, the Cancer Registries covered only the northern and central provinces. In addition, the Cancer Registries did not publish separate figures for CLL, choosing instead to combine it with acute lymphatic leukemia in the lymphoid leukemia group, consistent with the format of the IARC Cancer Incidence in the Five Continents (CI5C) reports [47]. Therefore, the database we used is a unique source of information that is valuable for understanding the time and space coordinates of specific hemolymphatic malignancies. Moreover, the same senior hematologist personally reviewed all diagnoses, thus preserving the comparability of data collected over three decades. This procedure is advantageous compared with similar surveys, as it allows the error to spread uniformly over time and space, thus preventing interobserver variations in applying the diagnostic criteria.

We cannot exclude that, particularly in the first period of the active search of incident cases, the local physicians might have increased their awareness and reporting of the less-aggressive CLL forms. This might have been the case, especially for elderly patients, whose natural aging process might have prevented conducting in-depth diagnostic workups. An upgrade of the diagnostic capabilities and widespread proliferation of well-equipped laboratory facilities in those years might also have contributed, along with the concurrent easier access to hospitals and specialist care due to upgrades in the public and private transport and the road network. Overall, these conditions might have resulted in increased reporting of CLL, thus generating a spurious upward trend. Indeed, CLL risk was elevated for those residing 30 km or more from the nearest hospital, suggesting that uneven access to health care over the Sardinian territory for diagnosis and treatment of nonmalignant diseases possibly conveying an elevated CLL risk might have played a role. Such a finding did not reflect the results of the analysis of social deprivation, which did not show an association. However, the continuous upward trend in CLL confirmed that for NHL [18] and MM [28] and contrasted what was observed for myeloid malignancies [Broccia G et al., 2023, submitted], which would exclude that such bias affected specifically our CLL results. The information on the commune of residence at the time of diagnosis was missing for 51/1700 patients (3.1%); it seems unlikely that this might have affected the geographic patterns or the analysis of time trends.

The validity and completeness of the database we used were previously tested by comparing the results with cancer registry data in selected areas and time windows [18]. Our analysis of environmental risk factors was an ecologic analysis, which considers the population of each commune and not the individual as the unit, thus exposing it to possible false associations due to the ecologicfallacy [48]. On the other hand, the time and space coordinates of neoplastic diseases can generate hypotheses on associations with widespread risk factors, reflect underlying changes in the diagnostic classification, and measure the effectiveness of therapeutic advancements [49]. Therefore, while stressing the public health relevance of our findings, we recommend caution in interpreting our results.

CONCLUSIONS

Our findings suggest that multiple possible environmental factors typical of urban areas, such as increasing vehicle emissions and crowding, and others related to rural residence and activities, along with improvements in access to health care facilities and diagnostic capability, especially in the case of indolent forms, might have contributed to the global upward trend in CLL incidence. Further studies shall address the genetic and environmental determinants of CLL and their interaction.

Conflict of Interest Disclosure

The authors do not have any conflicts of interest to declare about this work.

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Data Availability

Data are stored on the figshare repository and are publicly available (doi: 10.6084/m9. figshare.23576433).

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