

Incidence of non-Hodgkin's lymphoma and Hodgkin's disease in Sardinia, Italy: 1974-1993

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Background and Objectives. The reasons for the worldwide increase in non-Hodgkin's lymphoma (NHL) are not clearly understood. We investigated whether an increasing trend over time has also occurred in the Italian region of Sardinia, the population of which exhibits peculiar genetic features, due to millenary isolation and pressure from 2,500 years of malarial endemism. We also investigated the geographic variation in NHL risk within the region.

Design and Methods. We designed a descriptive epidemiology study of NHL among the Sardinian population by following up the incidence of this disease in the period 1974-1993. We calculated the standardized incidence rate (SIR) of NHL by year for the total population and by gender. The time trend of Hodgkin's disease (HD) was also evaluated as a comparison term and for validation purposes. We also mapped NHL risk in the 361 administrative units (communes) of the region.

Results. NHL incidence in the Sardinian population over the whole study period was 7.5×10^{-5} year⁻¹ (men: 8.2; women: 6.7), and increased from 4.1 in 1974 to 9.1 in 1993. The increasing trend was consistent by gender, and mostly affected subjects aged 55 years or older. Nodal and extra-nodal forms of NHL shared the same pattern of increasing incidence. Excluding the few NHL cases related to AIDS did not change the results. No such pattern was observed for HD incidence. The NHL incidence rate (age ≥ 25 years) ranged from $0.0-60.0 \times 10^{-5}$ year⁻¹ across communes. Areas at risk were located mainly in the northern part of the region, but risk among men was also elevated in the major urban area in southern Sardinia.

Interpretation and Conclusions. Our study shows that NHL incidence increased 2.2-fold in Sardinia from 1974 to 1993, a finding which is consistent with other worldwide report. The risk has risen in a few areas, mainly in central and northern Sardinia and in the major urban areas. Analytic studies are under way to investigate a broad range of risk factors, including viral, occupational, and environmental factors, that might account for our results.

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In most developed countries, the incidence of non-Hodgkin's lymphoma (NHL) is increasing steadily at an annual rate of approximately 4%, indicating a doubling of incidence every 20 years.¹ Apart from rare exceptions, this trend appears to be consistent by gender and by nodal and extra-nodal forms of NHL.¹ The reasons for such an increasing trend have been widely discussed, and it is possible that improvements in diagnostic procedures explain part of it, particularly in the elderly. However, it is now accepted that it also reflects a real increase in the incidence.² The population of the Italian region of Sardinia exhibits peculiar genetic features, due to millenary isolation and pressure from 2,500 years of malarial endemism. Genetic studies based on the frequency of 42 alleles have shown that there is a considerable genetic distance between the Sardinian population and any other known population in Europe, including the other Italian populations, or Africa, while a certain homogeneity exists among populations from various areas of Sardinia.³ Genetic drift, i.e. variations in the gene frequency due to random fluctuations, is supposed to be the main reason for such differences, as a very limited number of genes has been added to the aboriginal population, in spite of numerous invasions and conquests. These peculiarities are reflected by the atypical frequency of some alleles, such as the lowest Rh- prevalence in the Mediterranean area (20%), and the highest world prevalence of the Diaforase-2 and HLAB*8 genes, as well as genetic blood disorders such as G6PD deficiency and thalassemia, and an unusually high prevalence of diseases such as childhood type 1 diabetes mellitus or non-AIDS related Kaposi's sarcoma.⁴ These genetic peculiarities raise interest in the epidemiology of NHL over time in Sardinia. Mapping NHL risk by local administrative units may also help to understand whether geographic variation in risk persists within a population with similar genetic features and dietary patterns, such as the Sardinian population.

Design and Methods

Currently, Sardinia is only partially covered by a Cancer Registry, which started operating just recently.

Therefore, the registries of local pathology departments are the only available source of historical information about cancer cases. These registries include all first diagnoses of incident cancer cases among the resident population, as diagnosis is made locally even for most patients seeking care from specialized centers in the rest of Italy or abroad. We extracted individual data of all cases with a pathologic diagnosis of defined or suspected lymphoma between January 1, 1974 and December 31, 1993 from all Pathology Departments in Sardinia. These records were matched with clinical data from medical, surgical and pediatric departments of admission to revise the diagnostic criteria. Such a procedure prolonged the phase of data collection, but allowed us to include a few cases who had a pathologic diagnosis made outside the region and subsequent hospital admissions in Sardinia, and to exclude leukemia cases misdiagnosed as lymphoma. Over the 20-year period covered in this study, a few lymphoma classifications came in use which identified NHL as a single disease with peculiar morphologies and clinical behaviors. The Rappaport classification, the Luke-Collins and the Kiel classifications were replaced in the middle 1970s by the Working Formulation, developed by an international collaborative group to make it possible to compare clinical trials and to conduct international analyses.⁵ More recently, the introduction of immunophenotyping and genetic techniques allowed the recognition of a number of distinct disease entities, upon which the *International Lymphoma Study Group* reached consensus in constructing the *Revised European-American Classification of Lymphoid Neoplasms* (REAL). This classification identifies and includes also the so-called mucosa-associated lymphoid tissue (MALT) tumors, which were not recognized or not specifically listed in the previous classifications.⁵ These changes were reflected among the various pathology departments in Sar-

dinia along the study period, but they were introduced at different times by the individual pathologists. Unfortunately, pathology slides were largely unavailable for us to conduct a systematic review in order to uniform the various histologic classifications. To prevent difficulties in comparing data coded using different ICD-O versions, the *International Agency for Research on Cancer* (IARC) Atlas of Cancer Incidence in Five Continents defined NHL as the grouping of the ICD-9 codes 200 and 202.⁶ The definition of NHL in our study is consistent with the IARC definition, which allowed us to overcome the above mentioned difficulties and to compare our retrospective reconstruction of NHL incidence with those from the various Italian Cancer Registries. However, we could not explore time trends and spatial distribution of NHL by histologic subtypes or grade of malignancy.

Based on these data, we reconstructed incidence of NHL and Hodgkin's disease among the Sardinian population from 1974 to 1993. The temporal trends of nodal and extra-nodal forms of NHL were explored separately. However, this analysis was restricted to adult cases (aged 25 years or more) identified in the Cagliari province, as the retrieval of clinical records to discriminate nodal from extranodal forms of NHL was incomplete for the other provinces in the early years of the study period. We calculated the standardized incidence rate (SIR) of NHL in 1974-1993 by year and over the whole study period for the total Sardinian population (1.7 million at the 1991 Census), by gender and selected age-groups (0-24, 25-54, 55-74, and 75 years or more), and for each one of the 361 local administrative units (communes) from age \geq 25 years, using the 1981 census Sardinian population as the standard. As a comparison term and for validation purposes, the same analysis was conducted on HD cases occurring along the same time period.

Finally, we calculated the relative risk (RR) for NHL

Table 1. NHL and HD incidence rates ($\times 10^{-5}$ year⁻¹) in Sardinia, Italy: 1974-93.

<i>Non-Hodgkin's lymphoma</i>												
											Age-specific rates	
Gender	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	CIR	SIR*	SIR ^o
Male	0.9	1.5	1.3	2.4	6.1	8.9	18.2	27.3	25.6	7.0	8.2	6.0
Female	0.6	0.7	1.1	1.8	3.6	8.4	11.7	22.2	19.2	5.8	6.7	4.4
Total	0.7	1.1	1.2	2.1	4.9	8.6	14.8	24.6	21.9	6.4	7.5	5.2
<i>Hodgkin's disease</i>												
											Age-specific rates	
Gender	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	CIR	SIR*	SIR ^o
Male	0.1	1.0	2.8	4.7	3.3	3.4	4.0	3.4	2.9	2.9	2.8	2.7
Female	0.0	0.5	3.0	4.4	2.4	2.5	1.5	2.3	1.6	2.2	2.2	2.0
Total	0.05	0.7	2.9	4.5	2.9	3.0	2.7	2.8	2.2	2.5	2.5	2.3

CIR = crude incidence rate; SIR = standardized incidence rate. *Standard population: regional population at the 1981 census. ^oStandard population: world standard population.

and its 95% confidence interval in each commune, as the ratio between observed and expected cases. Expected cases in each commune were calculated by applying the 10-year age-group- and gender-specific incidence rates of the Sardinian population to the person-years in the corresponding strata, and by summing the results over the strata.

Results

Overall, we identified 1,877 incident cases of non-Hodgkin's Lymphoma along the study period, 1,023 among men and 854 among women, with a 1.2:1 male/female ratio. There were 803 cases of Hodgkin's disease, 452 among men and 351 among women. Table 1 shows the gender- and age-specific incidence rates for NHL and HD. Unlike HD, the incidence of NHL showed a sharp increase up to age 65-74, and a partial decline in the eldest age-group. This pattern was consistent by gender. The NHL incidence rate over the whole study period was 7.5×10^{-5} year⁻¹ in the total population, 8.2 among men, and 6.7 among women, when the 1981 Census regional population was used as the standard. The NHL incidence rate increased in 1974-1993 in both genders (Figure 1); for the total population, the incidence in 1993 (9.1×10^{-5}) was more than double that in 1974 (4.1×10^{-5}), consistent with international data. The average annual increase in the NHL rate was 6.1% for the total population, and was more pronounced among men (6.8%) than among women (6.0%). No such pattern was observed for HD incidence. These time trends in NHL incidence and HD incidence match those observed from mortality data in 1980-1994, as extrapolated from the published annual health statistics reports of the *Italian Central Institute for Statistics* (ISTAT) for the purposes of this study. The NHL mortality rate for the total Sardinian population increased almost two-fold from 2.6×10^{-5} in 1980 to 4.9×10^{-5} in

1994, while HD mortality rate was 0.8×10^{-5} in 1980 and 1.0×10^{-5} in 1994, ranging from 0.5 - 1.3×10^{-5} along the study period, with wide annual variations. Mortality from all cancers also increased in Sardinia from 147.2×10^{-5} in 1980 to 220.4×10^{-5} in 1994, at a higher annual rate than among the total Italian population, the rates for which were, respectively, 217.6×10^{-5} in 1980 and 274.1×10^{-5} in 1994.⁷ Of the individual cancer sites, lung cancer and leukemia (lymphatic and myeloid acute and chronic types combined) showed an increasing trend from, respectively, 26.8 and 6.5 in 1980 to 42.0 and 8.2×10^{-5} in 1994. On the other hand, mortality from stomach cancer and cardiovascular diseases decreased from, respectively, 16.1 and 368.3×10^{-5} in 1980 to 11.9 and 342.9×10^{-5} in 1994. Mortality from non-malignant respiratory diseases and diseases of the digestive system did not vary along 1980-1994.⁷

The analysis of trends in NHL incidence by specific age-groups is shown in Figure 2. NHL incidence increased significantly among subjects aged 55-74 years ($r = 0.891$; $p < 0.001$) and 75 years or more ($r = 0.846$; $p < 0.001$). A modest upward trend was also observed among subjects aged 25-54 years ($r = 0.664$; $p < 0.01$): the incidence in 1993 (6.9×10^{-5}) was approximately 75% greater than that in 1974 (3.9×10^{-5}). We did not observe any increase below the age of 25. Clinical records in the early years of the study period were fully available only for the 595 cases aged 25 years or more identified in the Cagliari province. Therefore, the comparison of the time trend of nodal and extra-nodal forms of NHL was restricted to these subjects. The incidence rate of both forms seems to increase along the study period, although with large annual variations due to the small numbers of observed cases per year (not shown in tables and figures). A total of 13 cases of NHL, occurring in seven men and six women, were identified among patients affected by AIDS (0.7%). All cases occurred from 1984 onwards. Excluding

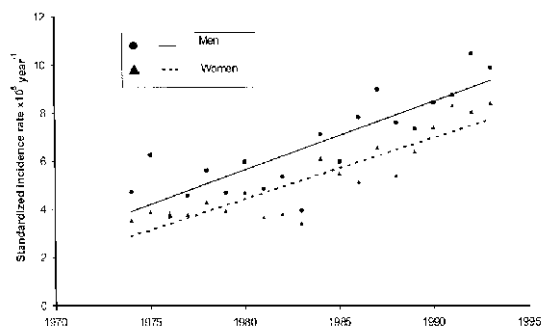


Figure 1. 1974-1993 incidence of NHL in Sardinia, Italy (all ages, by gender).

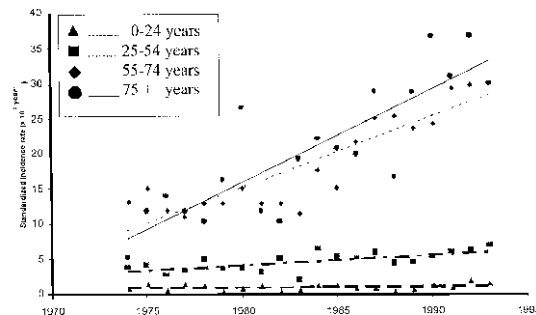


Figure 2. Time trend of NHL by specific age-groups in Sardinia, Italy (male and female, combined).

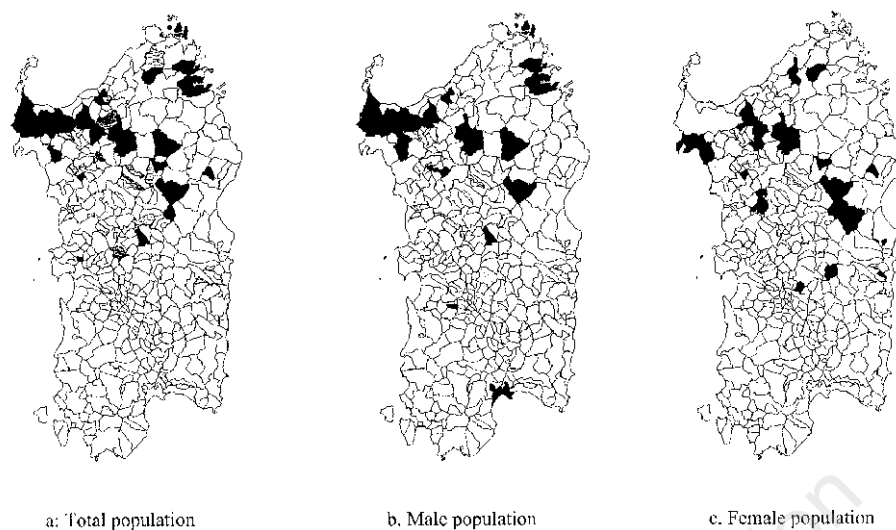


Figure 3. Map of the relative risk of NHL in Sardinia, Italy (age ≥ 25 years).

these cases did not change the increasing trend of incidence rate of NHL over time.

The incidence rate of NHL (age ≥ 25 years) varied across communes within the range $0.0-60.0 \times 10^{-5}$ year $^{-1}$. The maps of the relative risk (RR) of NHL by commune are shown in Figure 3. The darkest spots are communes with a statistically significant increase in risk. Grey spots are communes with $RR \geq 1.5$, based on at least 3 cases, not reaching statistical significance. Areas at risk are clearly located mainly in central and northern Sardinia, although, among men, an elevated risk was also observed in the main urban area in southern Sardinia. Among 18 communes with a significant increase in risk for the total population, six confirmed the same significant excess also in the first decade (1974-1983), while five manifested the excess only in 1984-1993.

Discussion

Our results confirm that, also in the Italian region of Sardinia, the incidence rate of NHL has approximately doubled over the 20-year period between 1974-93. The increasing trend was consistent by gender, although more pronounced among men, and independent of the AIDS epidemic. Both the nodal and extra-nodal forms of NHL increased over the study period, although this analysis was restricted to part of the study area. NHL risk concentrated mainly in northern Sardinia for the total population and in the major urban areas among men. The analysis of mortality data confirmed the increasing trend in NHL contrasting with the absence of a similar pattern for HD mortality. This phenomenon occurred within the general tendency of an increase in cancer mortality, and particularly lung cancer and leukemia, in 1980-1994, at a higher annual rate in Sardinia than in the rest of Italy.

On the other hand, mortality from stomach cancer and cardiovascular diseases showed an inverse trend.

Our findings are consistent with reports describing increasing trends of approximately the same magnitude in other countries worldwide, mostly in middle and old age, and more pronounced among men. An annual increase of 3.2% per year in 1973-95 was recently reported to have occurred in Metropolitan Detroit, Michigan, USA.⁸ Consistently with our findings, all age groups but the very young (ages 0-19 years), were affected. The NHL epidemic in Metropolitan Detroit was generalized and not confined to specific genders or racial groups or major histologic types.⁸ An overall annual increase in NHL incidence of 4.2% was also reported in Europe in 1985-92, being more pronounced among men (4.8%) than among women (3.4%),⁹ consistent with our findings and another report.¹⁰ As confirmed in our study, middle and old age groups were mostly affected. Inter-country differences were also observed, with highest rates in the Scandinavian countries and the Netherlands.⁹ The average annual increase in NHL incidence was greater and not explained by the AIDS epidemics in two Spanish areas (5.8%),¹¹ and in Côte-d'Or, France (6.8%).¹⁰ The French study suggested a greater increase for low-grade and high-grade NHL compared to intermediate-grade NHL.¹⁰ However, this finding is not comparable with the USA report, in which intermediate and high-grade NHL were considered jointly.⁸ Geographic variation in risk,^{8,9} the lack of similar time-related increases among the youngest ages,^{8,9,11,12} and the steeper slope among the male gender^{9,10} suggest that environmental exposures of unknown nature occurring during young or adult life

might account for the worldwide increasing trend of NHL. Our results are consistent with these reports, giving more strength to the hypothesis. As the region of Sardinia is not yet fully covered by a Cancer Registry, concern about the completeness of data collection and, therefore, the exact size of the annual increase might arise. The fact that we did not observe a similar increasing trend for HD incidence over time suggests that uncertain completeness of data collection or diagnostic improvements along the study period do not substantially affect the results. The list of incident cases was manually reconstructed by consulting the registries of all Pathology units in the region, which are the first to make a new diagnosis of a malignancy. Cancer patients seeking specialized medical assistance outside the region are surveyed by the Health Department of the Regional Administration, which supports them with financial aid when local Health facilities cannot timely provide a similar type of care (*Health Department of the Regional Government of Sardinia, personal communication*). The same Health Department made its archives available for the purposes of this study. Therefore, coverage of new diagnoses in the study period is expected to be very close to complete. An attempt to validate a similar retrospective procedure for assessing childhood leukemia incidence by comparing the calculated incidence rates with those estimated from mortality and survival rates, showed that no substantial loss of cases occurred due to the retrospective procedure.¹³ We have no reason to suspect that such an event occurred in the present study, although we cannot exclude it. To validate our procedure further, we compared the NHL incidence rate in Sardinia in 1988-1992 (age 0-74 years, world standard population) with those reported in the 13 Italian Cancer Registries covering various periods in the corresponding years.⁶ Sardinian rates ranked 11th among men and among women, with rates comparable to those reported in the Cancer Registries of Central and Southern Italy. This comparison further suggests that the incidence rates of NHL herein reported were not affected by a significant loss of cases. Another weakness of our study, also due to its retrospective nature, is that original slides were not available to evaluate patterns by histologic types and grade of malignancy. However, that the late inclusion of MALT tumors in the lymphoma classification might fully account for the increasing temporal trend does not seem likely. In fact, the increasing trend was observed in nodal forms of NHL as well as in extra-nodal forms, which include a greater proportion of MALT-type tumors. Also, the increase in NHL incidence was greater among the eldest age-groups, in which the proportion of MALT tumors is highest, but a significant increasing trend was observed among subjects aged 25-54 years as well. Finally, the increasing trend became sharper in the early 1980s before MALT lymphoma was described.¹⁴ The REAL classification was published in 1994,¹⁵ one year later than the last year of incident data collection in our study, and, therefore, could not have affected our results. We conclude that,

while it is plausible that changes in NHL classification and the identification of new disease entities along the study period might have contributed to generate the increasing trend, it is unlikely that they fully account for the 2.2-fold increase we observed over the 20-year study period.

We have no explanations for the peculiar geographic distribution in NHL risk that we observed. The Sardinian population is genetically homogenous and shares very similar dietary habits. We cannot discard the possibility of spurious increases in risk related to the elevated number of comparisons we made. However, assuming a chance effect, we would have expected a random distribution of high risk areas over the regional territory. Instead, we observed their concentration in northern Sardinia, which matches that reported in the Atlas of Cancer Mortality in Sardinia for the years 1983-1987 among women.⁴ On the other hand, while in that Atlas, NHL risk among men was non-significantly elevated in the southern areas of the region, designing an improbable gender-specific geographic distribution in risk, no such a pattern was visible in our study of incident data. Alternatively to chance, viral, occupational, and environmental risk factors might account for our results. Analytic studies are under way to explore, in detail, the role of these factors and their interaction in the etiology of NHL.

Contributions and Acknowledgments

GB promoted the study, acquired incidence data, reviewed pathologic and clinical records, and revised the manuscript. PC performed the epidemiological analysis and wrote the manuscript. PCa assisted in data management and manuscript revision.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was been peer-reviewed by two external referees and by Dr. Paolo G. Gobbi who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Gobbi and the Editors. Manuscript received June 15, 2000; accepted November 15, 2000.

Potential implications for clinical practice

This work is of paramount importance for planning health care implementation for NHL patients over the region of Sardinia. Also, future studies on the effectiveness of therapeutic protocols on survival of NHL and HD patients may rely on its data-base.

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