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Incidence of malignant lymphoproliferative diseases by stage and histological variants in Central Italy: a population based study 1982-1994

G. DI LEONARDO, P. TORCHIO*, E. PASQUALONI, G. CORRAO*, D. QUAGLINO

Department of Internal Medicine and Public Health – University of L'Aquila (Italy)
**Institute of Statistical and Mathematical Sciences – University of Milan (Italy)*

Abstract. – **A population-based epidemiological study that concerns the estimate of incidence rates of Hodgkin's Disease (HD) and Non Hodgkin's Lymphoma (NHL) in a Central Italy area was performed. All the new cases of HD and NHL diagnosed from 1982 till 1994 in the target population were collected by multiple information sources. The temporal trend of incidence rates and their relation with age, gender and histological variant were analyzed. In the considered period 95 cases of HD and 297 cases of NHL were collected. Constant age-adjusted incidence rates of HD were observed, while an increasing trend of NHL incidence rates was observed especially for cases at presentation in stage III and IV and for histotypes G, H and I.**

The investigations carried out on patients with HD have shown that this condition prevails in women in the younger age groups, while in men presentation occurs more frequently at an advanced age. Moreover the authors have confirmed previous reports of a distinctly increased incidence of nodular sclerosis in contrast to the other three histological variants which do not show a juvenile peak but a gradual increase in incidence with advancing age.

The epidemiological features of NHL's observed correspond to the standard incidence rates obtained in Europe and throughout the world. NHL's appear to be a pathological entity typical of elderly patients: however high-grade NHL's, in contrast to low-grade NHL's, was present with increased frequency also in childhood and in patients under the age of 30.

Key Words:

Lymphoproliferative disease, Hodgkin's disease, Non Hodgkin's lymphoma, Incidence.

Introduction

Malignant lymphoproliferative diseases (MLD), including Hodgkin's Disease (HD) and Non-Hodgkin's Lymphoma (NHL), are among the most perplexing diseases[1]. Their aetiology remains poorly understood but is currently accepted that both environmental and genetic factors interact in the occurrence of these diseases[2].

Descriptive epidemiology, including the study of geographical variations, temporal trends, age and gender distributions in the incidence of HD and NHL and in its histological variants, might help to generate hypothesis of some of the factors involved in the aetiology of MLD[3].

Incidence of these diseases shows noticeable regional variations. Rates from 0.1 to 5.0 new cases of HD and from 0.4 to 17.4 new cases of NHL per 100,000 inhabitants have been reported by population-based cancer registries[4]. Different temporal trends of age-adjusted incidence rates of MLD, with slightly declining numbers of HD[5] and increasing figures of NHL[5-7], have been observed. Furthermore, age and gender incidence patterns, expecially of HD, present noticeable geographical and temporal variability[8]. Probably, stage presentation and histological variants have an important role in explaining these differences[9], but population based cancer registries do not report histological informations.

On the basis of these considerations, a descriptive epidemiological study was conducted with the aim to explore the sources of variability of incidence rates in this well defined Italian area where the histological monitoring of all the new cases of MLD was performed since 1982 with standardised criteria.

Subjects and Methods

Population and study area

This population based incidence study was carried out in an Italian province (Teramo; Central Italy) with resident population varying from 269,400 inhabitants in 1982 to 279,800 in 1994. This population accumulated a total of 3,609,900 person-years of observation.

Estimates of the resident population were obtained from the Italian Central Institute of Statistics and tabulated by year (1982-1994), sex and 10-year age strata[10-11].

Case findings

Case material consisted of all new diagnoses of malignant lymphoproliferative diseases occurring from January 1982 to December 1994 in the population resident in the covered area.

Potential cases were identified considering all the public and private services involved in the diagnosis and treatment of MLD. New diagnoses performed during the study period were collected from: (1) active flagging of pathology services and haematological and medical divisions situated in the study area; (2) research in regional discharge archives of the same and of the neighbouring regions; (3) research in diagnosis and treatment archives of the National Cancer Institutes. In addiction, all general practitioners of the considered area were asked to provide information regarding MLD among their patients. Patients diagnosed outside the study area but resident within it, were included in the study. Conversely, we excluded from the study patients diagnosed within the study area but resident elsewhere. Diagnosis made before the study period were also excluded.

Diagnostic criteria

All patients included in the study were untreated and diagnosis was based on biopsies obtained principally from lymph nodes, but also from the stomach, the gastrointestinal tract, the spleen and the kidney.

Bioptic material was processed according to standard histological stains (Haematoxylin-eosin) and during the last 6 years immunohistochemical techniques were applied to all histological sections available. In almost all the cases included in the study before 1989, diagnosis was re-evaluated in the light of the new histological classifications and with the aid of supplementary immunohistochemical stains.

Histological classification of HD was based on the proposals of the Ann Arbour Workshop[12] according to which cases were subdivided into four subgroups: lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte depletion (LD). Clinical staging was established on the basis of the Ann Arbour staging[12]. Among the lymphatic structures are included lymph nodes, the spleen, and the thymus, the structures of Waldeyer's ring, the appendix and Peyer's patches. Each stage was further subdivided according to the absence or the presence of defined general symptoms (weight loss, fever, night sweats).

As far as NHL's are concerned, cases were classified according to the Working Formulation[13]. In the miscellaneous group (group K of the Working Formulation) were included both low-grade cases, such as CTCL as well as high-grade NHL, such as Ki-1 and histiocytic lymphomas; lymphomas from the gastro-intestinal tract were uniformly classified as Mucosal Associated Lymphoid Tissue (MALT).

Statistical analysis

Age adjusted incidence rates have been calculated using the world standard population as reference (direct standardisation). The 95% confidence intervals (CI), assuming a Poisson distribution of observed number of cases, were computed[14]. The Mantel-Haentzel test for the comparison between two strata-specific rates was applied[15].

The sources of variability of the observed incidence rate, were investigated by means of fitting a Poisson's multiple regression model[14]. This last considered the incidence rate as the dependent variable, and gender, age and period as the independent variables. The maximum likelihood estimate of the relative risk (RR) and the corresponding 95% CI for each level of independent variables were also cal-

culated. These data were performed using the GENMOD procedure of the SAS package[16].

Results

Hodgkin's disease

From January 1982 till December 1994, 95 new cases of HD were identified. Fifty eight cases were men and thirty seven women with gender ratio of 1.57. Mean age at diagnosis (± standard deviation) was 40.2 (± 19.8) years. Stage I was present in 7 cases (7.4%), stage II in 43 cases (45.3%), stage III in 30 cases (31.6%) and stage IV was observed in 14 cases (14.7%). The following histotype variants were found: lymphocyte predominance in 12 cases (12.6%), nodular sclerosis in 52 cases (54.7%), mixed cellularity in 24 cases (25.3%) and lymphocyte depletion in 6 cases (6.3%). Fifty seven patients (60.0%) presented definite clinical symptoms at diagnosis. Finally, stage, histotype and symptomatology were unknown for one patient. With the exception of stage I, nodular sclerosis histotype appeared more frequently associated with clinical symptoms than the other histological subtypes. The different histotypes were distributed quite evenly among the different clinical stages although lymphocyte depletion histotype was often associated with generalised symptoms.

In the overall period the average age-adjusted incidence rate was 3.3 per 100,000 per year in men and 2.1 per 100,000 per year in women.

Figure 1 shows the trend of the annual incidence rates. Although the incidence estimates were unsteady, a progressive decrease during the last years of observation was noticed. The age-specific incidence rates showed a bimodal distribution, with a maximum peak around the second decade of life and a second relative peak between the fifth and sixth decade (Figure 2). The first peak was clearly present in women while the second one appeared only in men. However, mean age at diagnosis did not significantly differ between genders (mean age = 36.2 ± 18.8; range 16-83; and mean age = 42.7±20.2 range 5-84; in men and women respectively, t test for independent samples: t=1.65; p = 0. 11). Homogeneity between gender was also observed for distribution of histotypes: nodular sclerosis accounted for 50% and 58% of cases in men and women respectively.

Figure 3 shows the distribution of HD incidence rates according to age and histological subtypes. Nodular sclerosis histotype was

Figure 1. Age adjusted incidence rates from Hodgkin's disease for men and women between 1982 and 1994.

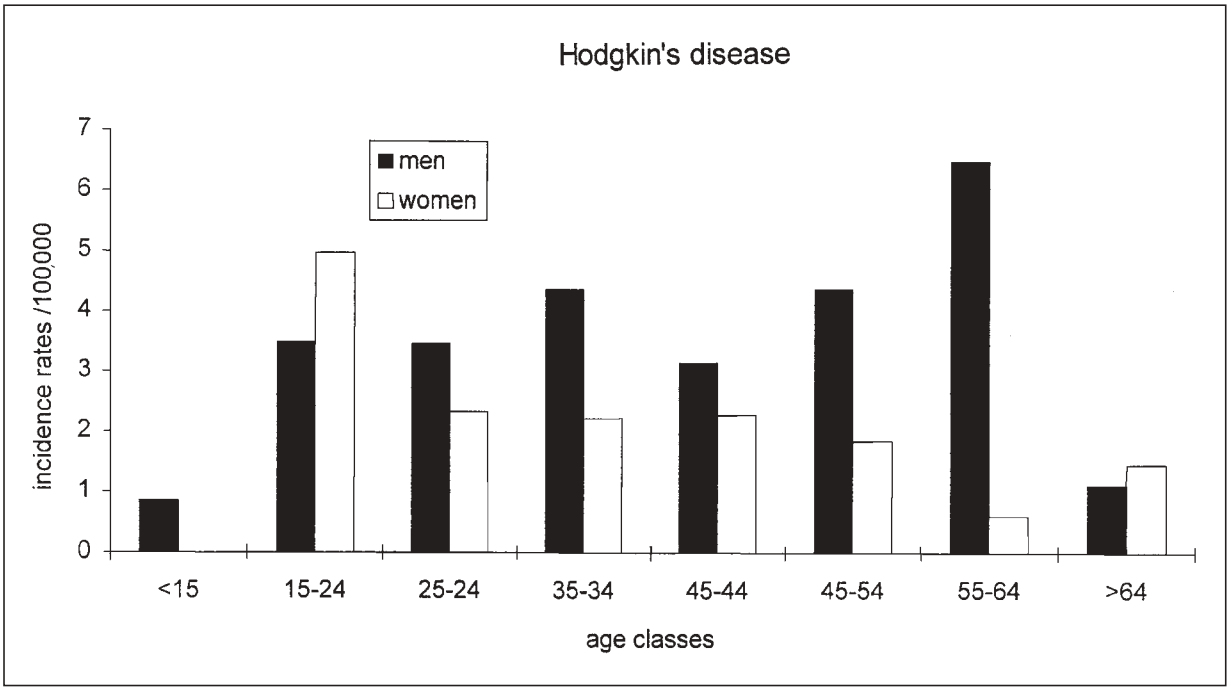

Figure 2. Incidence rate by age from Hodgkin's disease for men and women between 1982 and 1994.

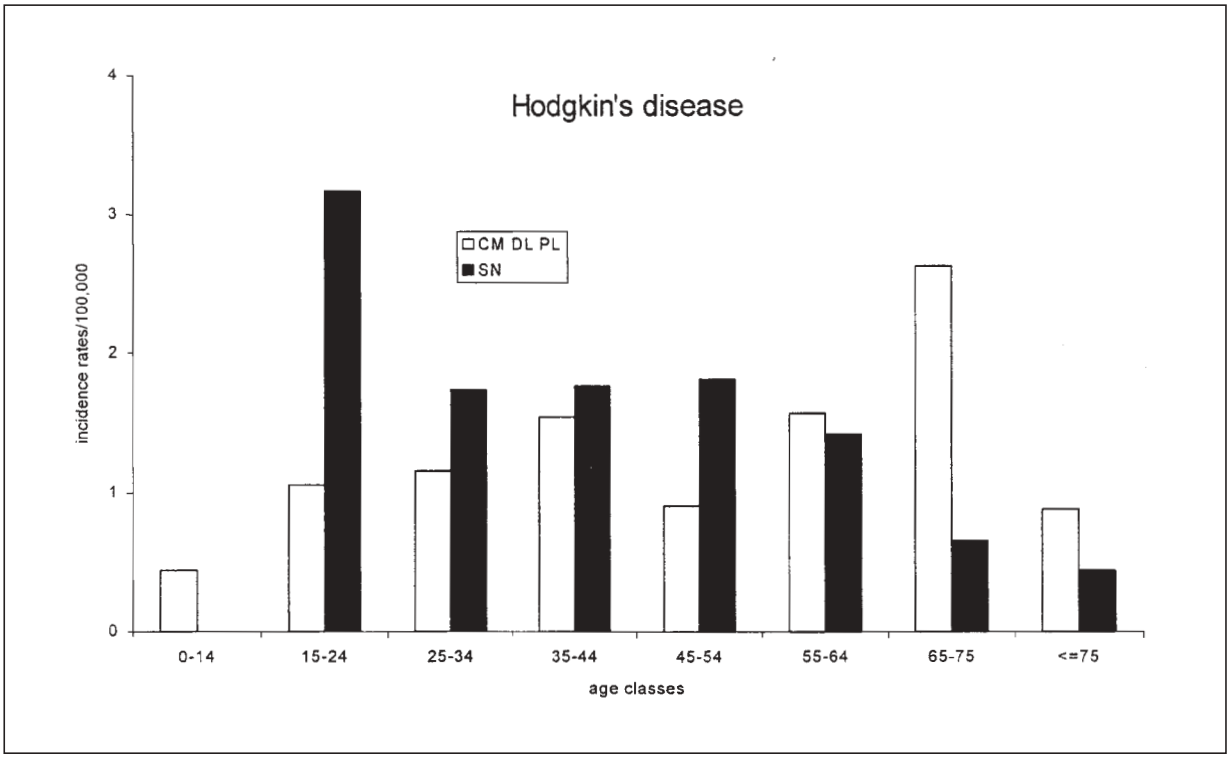

Figure 3. Incidence rates by age from Hodgkin's disease: histological variants for men and women between 1982 and 1994.

Table I. Hodgkin's disease standardised incidence rates in two observation periods by stage, histological characteristics and symptomatology.

	1982-1987 period			1988-1994 period			
	Cases	Rates[a]	95% Ci[b]	Cases	Rates[a]	95% Ci[b]	Z[c]
Stage							
I	0	0.00	–	7	0.34	0.08-0.59	2.38*
II	25	1.44	0.86-2.02	18	0.92	0.49-1.35	1.66
III	16	0.87	0.43-1.31	14	0.59	0.26-0.92	0.93
IV	8	0.35	0.10-0.60	6	0.26	0.05-0.48	0.93
not known	0	0.00		1	0.06	<0 -0. 17	0.93
Histotypes							
lymphocyte predominance	9	0.51	0.17-0.85	3	0.13	<0 -0.28	2.03*
nodular sclerosis	21	1.15	0.65-1.65	31	1.52	0.97-2.06	0.72
mixed cellularity	15	0.84	0.39-1.28	9	0.40	0.13-0.67	1.74
lymphocyte depletion	4	0.16	<0 -0.31	2	0.08	<0 -0. 19	1.14
not known	0	0.00	–	1	0.06	<0 -0. 17	0.93
Symptomatology							
undefined	16	0.87	0.43-1.31	21	1.03	0.58-1.48	0.22
B	33	1.79	1.16-2.42	24	1.14	0.68-1.60	1.93
not known	0	0.00		1	0.06	<0 -0.17	0.93
Total	49	2.66	1.89-3.42	46	2.17	1.53-2.81	1.26

[a] standardized incidence rates calculated on world standard population.
[b] 95% confidence interval of rates.
[c] Z statistic calculated by a Mantel-Haentzel test, for the comparison of rates between periods.
* $p<0.05$.

more frequently diagnosed in younger ages. In contrast the other histological variants showed a higher incidence in the older ages.

Table I shows a weak and not significant decrease in HD incidence between the two considered sub-periods (from 1982-87 to 1988-94). However, a significant increase of stage I incidence rate and a significant decrease of the lymphocyte predominant histotype incidence rate were observed. No significant differences were observed after stratification for symptomatology.

Table II shows maximum likelihood estimates of the relative risk. HD risk in men was significantly higher than in women. No significant differences were observed between ages and periods.

Table II. Hodgkin's disease: relationship between observed incidence rates and gender, age and period.

Independent variables	Categories	RR[b]	95% Ci[c]
Gender	Women[a]	1.00	-
	Men	1.62*	1.07-2.44
Age classes	≤24[a]	1.00	
	25-44	1.44	0.86-2.43
	45-64	1.35	0.78-2.33
	≥65	1.19	0.61-2.31
Period	1982-1987[a]	1.00	
	1988-1994	0.77	0.52-1.16

* $p<0.05$.
[a] reference category.
[b] maximum likelihood estimates of the relative risk obtained by a Poisson's multiple linear regression model.
[c] 95% confidence interval of RR.

Non-Hodgkin's lymphomas

From January 1982 till December 1994, 297 new cases of NHL were identified. One hundred seventy one cases were men and one hundred twenty six women with gender ratio of 1.36. Mean age at diagnosis (± standard deviation) was 60.7 (±17.1) years. Stage I was present in 27 cases (9.1%), stage II in 59 cases (19.9%), stage III in 109 cases (36.7%) and stage IV in 102 cases (34.3%). The following grade of malignancy of the histotype variants were found: low grade (A, B, C) in 93 cases (31.3%), intermediate grade (E, F, G) in 74 cases (24.9%), high grade (H, I, J, K) in 90 cases (30.3%). CTCL (18 cases) and MALT (22 cases) were excluded from the count. Intermediate and high grade malignancy appeared more frequently associated with stage IV in contrast to low grade malignancy. Furthermore, clinical onset in stage IV was more frequent in men.

In the overall period annual average age-adjusted incidence rates of 9.2 per 100,000 in men and 7.0 per 100,000 in women were observed.

Figure 4, shows that the trend of the annual incidence rates progressively increased in both men and women.

Age-specific incidences showed progressive increase of the rates as age increases both in men and women (Figure 5). Mean age at diagnosis did not significantly differ between genders (mean age = 59.6±17.6 range 11-94 and mean age = 62.2±16.3 range 17-91 years in men and women respectively; t test for independent samples: t=1.34; p=0.18).

Table III reports the standardised incidence rates by stage and histotypes in the two subperiods (1982-87 and 1988-94). Increased incidences were observed for all stages, although only rates for stages III and IV were significantly higher in the second period. Similarly, with the exception of the C and J histotypes, increased incidences were observed for all the histotypes; however only G, H, and I histotypes showed rates significantly increased in the second period.

Table IV shows maximum likelihood estimates of the relative risk. Significant associations were found for gender, age and period with higher risk in men, in subjects older than twenty-five years and for the second period.

Discussion

Our study could not have captured all cases of newly diagnosed patients with MLD occur-

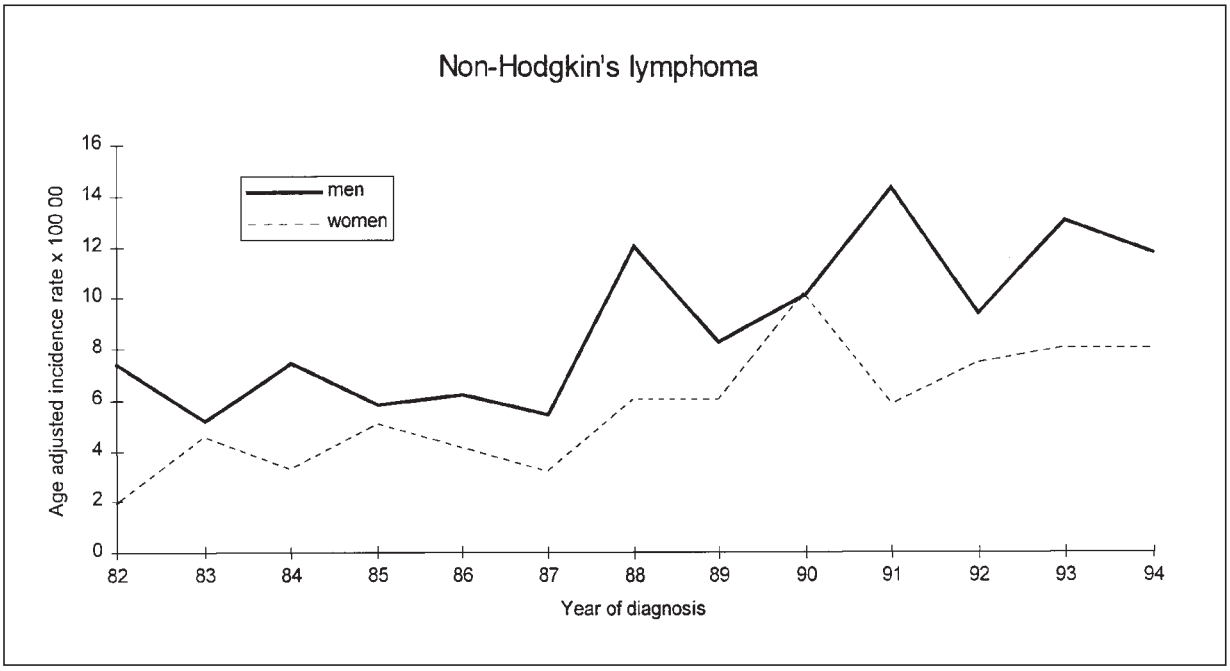

Figure 4. Age adjusted incidence rates from Non Hodgkin's lymphoma for men and women between 1982 and 1994.

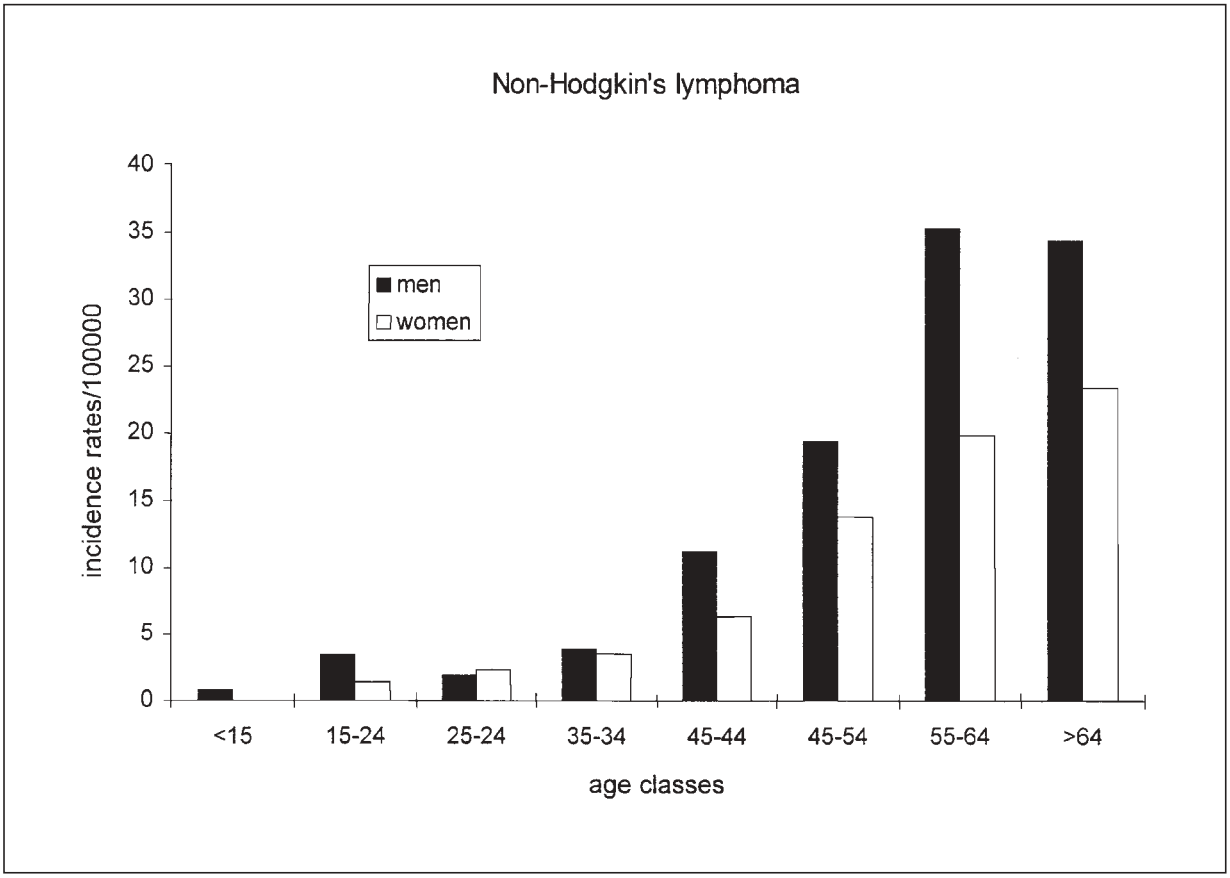

Figure 5. Incidence rates by age classes from Non Hodgkin's lymphoma for men and women between 1982 and 1994.

ring in the target population and the coverage level of capture could have been different during the observed period. However, we used multiple information sources including all medical services involved in the diagnosis and management of malignant lymphoproliferative diseases (medical and specialistic divisions, patology services and general practitioners) within the considered area. Moreover, we reached and included, whenever possible, also patients diagnosed outside from the study area, but resident within the area under study. Unfortunately, we were not able to use the capture-recapture methods because of the lack of independence of the informative sources used.

The hypothesis of a different coverage of our registration during the considered period, although plausible, seems unlikely since HD and NHL showed a different pattern of temporal trend.

Moreover, our incidence estimates were intermediate with those reported, for the same period, from the Italian population-based cancer registries. These last referred age adjusted incidence rates (100,000 per year) of HD ranged from 1.4 to 4.5 in men and from 1.2 to 4.0 in women while we found in men 3.0 and in women 2. Italian cancer registries reported, moreover, age adjusted incidence rates of NHL ranging from 5.5 to 12.4 in men and from 2.8 to 8.9 in women while we found in men 6.4 and in women 4.3. These data suggest that our coverage ability was at least comparable with that of the Italian cancer registries.

The most relevant findings which have emerged from our epidemiological study may be summarized as follows.

As far as HD is concerned, the study undertaken has confirmed that in our Region, as in the Western world, the most frequent histotype is NS (54.7%) and that patients with this histological variant were more frequently affected by general symptoms, compared to the other subtypes. In addition NS was more frequently observed in the younger age groups, while the other variants were more common in older pa-

Table III. Non Hodgkin's lymphoma standardised incidence rates in two observation periods by stage and histological characteristics.

	1982-87 period			1988-94 period			
	Cases	Rates[a]	95% Ci[b]	Cases	Rates[a]	95% Ci[b]	Z[c]
Stage							
I	7	0.31	0.07-0.98	20	0.67	0.35-0.98	1.88
II	19	0.78	0.41-1.66	40	1.23	0.81-1.66	1.80
III	28	1.23	0.75-1.71	81	2.67	2.05-3.28	3.81*
IV	33	1.33	0.86-1.80	69	2.34	1.74-2.93	2.36*
Histotypes							
A	24	0.91	0.53-1.29	43	1.25	0.85-1.65	1.26
B	5	0.22	0.03-0.42	12	0.44	0.18-0.70	1.29
C	4	0.17	0.00-0.35	5	0.16	0.01-0.30	0.03
D	5	0.21	0.02-0.41	13	0.51	0.22-0.80	1.45
E	2	0.06	<0-0.14	5	0.15	0.01-0.28	0.77
F	5	0.21	0.03-0.39	11	0.35	0.13-0.57	1.03
G	12	0.55	0.22-089	39	1,12	0.75-1.49	2.87*
H	7	0.28	0.06-0.50	28	0.93	0.57-1.30	2.85*
I	5	0.19	0.01-0.37	21	0.86	0.44-1.28	2.51*
J	4	0.22	<0-0.45	1	0. 03	<0 -0. 10	1.54
K	8	0.34	0.10-0.59	16	0.61	0.29-0.92	1.09
MALT	6	0.27	0.05-0.49	16	0.50	0.23-0.76	1.57
Total	87	3.65	2.85-4.45	210	6.91	5.90-7.91	5.06*

[a] standardized incidence rates calculated on world standard population.
[b] 95% confidence interval of rates.
[c] Z statistic calculated by a Mantel-Haentzel test, for the comparison of rates between periods.
* $p<0.05$.

tients. The existence of a bimodal distribution was also confirmed, but the first peak comprised mostly women, while the second peak, observed in the fifth and sixth decades affected predominantly males. During our period of observation there was a decline in the incidence of the lymphocyte predominance variant. Perhaps this latter subtype has recently been increasingly incorporated into NHL. Due to improved diagnostic procedures and greater clinical awareness on the part of physicians, there was an increase of presentation in the initial stages.

Another interesting finding which has emerged from our study is the particular age distribution of NS. Support for our results derives from an investigation carried out by the

Table IV. Hodgkin's lymphomas: relationship between observed incidence rates and gender, age and period.

Independent variables	Categories	RR[b]	95% Ci[c]
Gender	Women[a]	1.00	–
	Men	1.76*	1.40-2.22
Age classes	0-24[a]	1.00	–
	25-44	3.91*	2.14-7.14
	45-64	15.21*	9.12-25.37
	≥65	20.23*	12.61-33.45
Period	1982-1987[a]	1.00	
	1988-1994	1.83*	1.42-2.34

[a] reference category.
[b] maximum likelihood estimates of the relative risk obtained by a Poisson's multiple linear regression model.
[c] 95% confidence interval of RR.
* $p<0.05$.

Data Collection Study (DCS) of the Leukaemia Research Fund in Great Britain[17].

Also in this investigation the incidence figures were considered separately for the NS variant with respect to LP, MC, LD variants taken together.

The age incidence curve for NS showed a marked peak in young adults with little sex difference, declining rates at the age of 50 and a low stable rate subsequently. The age incidence for the other types showed, in contrast, a steady rise with age with only minimal evidence of the young adult peak and a three-fold male predominance.

This pattern suggests, according to the DCS study, the existence of two aetiological mecchanisms, the one probabily causing NS and responsible for the young adult peak, and the other causing chiefly MC but to a lesser extent also the LP and LD subtypes of HD.

The study of the Leukaemia Research Fund further suggested that the first factor could be linked to high socio-economic status and perhaps to residence near urban areas, both factors being associated with increased risk of disease in adolescence and early adult life. In regions more distant from built-up areas a lower incidence was found with few cases, especially fewer men in the young adult peak age.

In recent decades, many registries have reported slightly declining age adjusted incidence of HD among men and women. Temporal changes in diagnosis reliability and in differential diagnosis of MLD, although plausible, do not entirely explain the decline[9].

It has been reported that HD incidence has mainly decreased in older ages, whereas increases among young adults in some industrial countries have been observed. HD of the nodular sclerosis subtype has increased over time, whereas that of mixed cellularity has declined[18-20]. Improved therapy for HD has led to sharply declining mortality rates[5], but further understanding of the role of Epstein Barr Virus (EBV) and other possible causative agents (such as HIV) should afford opportunities for prevention[21].

With regards NHL's, hitherto there have been no many large scale national or international data available on the incidence of NHL's, subdivided by the Kiel Classification or other modern equivalents among unselected populations[22].

In our study patients with NHL compared to HD were usually found in a more advanced stage of the disease at diagnosis (stages III and IV). This is most likely due to the particular pathogenetic features which caracterize this type of malignancy, in which the disease, already at presentation, has a diffuse and widespread distribution in the lymphoid system.

Furthermore elderly patients are more subject to delays in initiating the necessary diagnostic procedures, with the consequence that, without adequate preventive measures, it is possible to expect a proportional increase of presentation in an advanced clinical stage.

Increased rates of incidence were found in older patients and relative risk was associated with gender, age and period of observation with higher risks in men, in subjects older than 25 years and in the second period of study, which showed an increased incidence of NHL's.

A study by Weisenburger[6] carried out between 1973 and 1989 showed that the incidence of NHL increased by nearly 60% in the United States. The annual incidence rates of NHL per 100000 persons in the United States has risen from 5.9 in 1950 to 13.7 in 1989. This increase occurred in both males and females, blacks and whites and in all age groups, except the very young. The largest increase has occurred in the elderly, and rates have increased more rapidly in rural areas.

When in our study NHL cases were divided between low- and high-grade disease, our data showed a similar trend to that obtained by the DCS of the Leukaemia Research Fund[17]. The total and age-specific incidence were studied for a five year period (1984-1988). In the DCS study low-grade NHL's did not show childhood cases. The first appearance of the disease emerged in the 15-19 age group, but the incidence rose sharply from early adult years. The median age of onset was 62 and 72% of cases occurred over the age of 55 with only 2% occurring below the age of 30.

With regards to high-grade NHLs the age-specific incidence differed sharply from that of low-grade and of all other lymphoproliferative states, except acute lymphoblastic leukaemia, in showing a substantial incidence in childhood, a much less steep rise with age. Nevertheless the disease is still predominantly found among the older age groups, the median

age of onset being again 62 and 72% of cases occurring over the age of 52, but in this group 9% of cases occurred below the age of 30.

In conclusion the results obtained from our study may not only provide information on the incidence of pathological conditions in relations to age, gender, annual incidence rates, histological pattern, but may also throw some light on possible aetiopathogenetic mechanisms which may underline the different distribution and incidence of the various histological and clinical subtypes.

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