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Research Article

Incidence, clinical characteristics and survival of malignant lymphomas: a population-based study from a cancer registry in northern Italy

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Abstract

We conducted a population-based study of peripheral lymphomas (PL) that had been diagnosed between 1997 and 2003 in the province of Modena, Italy, with the aim of providing updated incidence, clinical and survival data for these cancers. We evaluated the incidence patterns and time trends of 1582 cases of PL that had been reclassified according to the WHO classification of hematological malignancies. Data regarding clinical characteristics, treatment and outcome were also collected for each case. The World Age-Standardized Rate (ASR) was calculated as 13.4, 2.2 and 3.4 per 100,000 people for B-cell non-Hodgkin's lymphoma (NHL), T-cell NHL and Hodgkin's Lymphoma (HL), respectively, with an increase of 1.62% per year during the study period. The lymphoma subtype showing the highest incidence was found to be diffuse large B-cell lymphoma (DLBCL) with an ASR of 4.8. Compared with reports from other western countries, our series is characterized by a higher incidence of HL and indolent B-NHL in general, and of CLL/SLL (ASR = 3.3) and marginal zone NHL (ASR = 1.5), in particular, and also by a lower incidence of FL (ASR = 2). After a median follow-up of 54 months, the 5-year relative survival for the whole series was found to be 70% with a statistically significant improvement for cases diagnosed during 2002–2003 (from 66 to 74%; $p = 0.03$). Survival improvement within the study period was also evident for patients with DLBCL, HL and T-NHL. Our study provides a comprehensive description of both the epidemiological and clinical features of PL cases in Modena and our data also reflect the major advances in the curability of some histological subtypes of this disease. The usefulness of a population-based approach to better characterizing different lymphoma subtypes is also demonstrated. **Copyright © 2007 John Wiley & Sons, Ltd.**

Keywords: epidemiology; non-Hodgkin's lymphoma; Hodgkin's lymphoma; incidence; population-based study

Introduction

Peripheral lymphoma (PL) represents a heterogeneous group of neoplasms originating from an unknown stage of lymphocyte ontogenesis and is characterized by the accumulation or proliferation of mature lymphocytes; PL includes Hodgkin's lymphoma (HL), peripheral non-Hodgkin's lymphoma (NHL) and chronic lymphatic leukaemia [1]. Overall, HL and NHL represent the seventh most common cancer types in western countries, accounting for 3.6% of all malignancies [2]. Previous studies have shown that the incidence of NHL has increased in several regions worldwide over the past few decades, although the rate of increase has slowed recently [3,4]. The etiology of lymphoid neoplasms remains largely unknown, however, known risk factors include infections, treatments and diseases that cause severe immunosuppression [5].

Over the past 50 years there has been an important evolution in the classification systems used to categorize lymphoid neoplasms. According to the WHO classification of lymphoid neoplasms, which represent an evolution of the REAL classification system published in 1994, PL can be subdivided into more than 20 different clinico-pathological entities each characterized by a unique morphology, immunophenotype, cytogenetic and molecular features, clinical behaviour and some known etiological and pathogenic aspects [1].

The availability of such a reproducible classification system makes it possible to accurately classify PL into different clinical entities and to evaluate their incidence

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patterns. So far, however, there have been few comprehensive descriptions of the patterns and trends associated with lymphoproliferative diseases. For this reason, we have conducted a population-based study of all of the cases of PL diagnosed in the province of Modena, Italy, from 1997 to 2003. Each of these cases was diagnosed according to the WHO classification guidelines. The aim of our current study was to first evaluate the incidence patterns and trends for PL over time in general, and individually for each lymphoma subtype. Moreover, we provide a detailed description of the clinical characteristics, treatment approaches and outcomes associated with the different histotypes in our sample cohort.

Design and methods

Cases of PL that had been diagnosed over the 7-year study period from January 1st 1997 to December 31st 2003 were obtained from the Modena Cancer Registry (MCR). The MCR covers the population of the province of Modena, which is one of nine provinces in the Emilia-Romagna region of northern Italy. A 2001 census of this area indicates a population of about 634,000 growing by approximately 1% per year. The MCR was established in 1988 and is located in the Comprehensive Cancer Center of the University of Modena and Reggio Emilia. This registry obtains cancer diagnoses for all persons living in the Modena province via local pathology departments (registry of nodal, extranodal (EN) and bone marrow biopsies), from both local and national reports of hospital admissions and death certificates. The coverage achieved by the MCR can be considered excellent due to the low rate of death certificate only (DCO) reports (0.1%) [6].

For each case included in our current study the MCR provided data on patient demographics, histological type and primary cancer site. Histology was coded according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3), which is based upon the WHO classification of lymphoid neoplasms [1,7]. The diagnoses of PL and the ICD-O-3 codes were to be confirmed by a review of the original pathology report by three of the authors (S. L., A. M. and G. B.). When a histological subtype could not be confirmed by simply reviewing the original pathology reports, additional data were collected (i.e. cytogenetics, immunohistochemistry, cytofluorimetry and also molecular biology, clinical and laboratory data) to establish the correct ICD-O-3 code. In cases where sufficient data were lacking, a 'not otherwise specified' (NOS) category was assigned. For each histologically confirmed case chart review was also performed to collect additional data on disease characteristics (stage, sites of involvement), patient characteristics (performance status, systemic symptoms) and treatment modality, together with response assessments, when available, and patient's outcome. With regards to therapies, treatment was considered adequate if one of the following features was observed: (1) inclusion in a clinical trial; (2) receipt of a full dose of a standard polychemotherapy regimen for patients requiring therapy; or (3) limited radiotherapy and/or observation for patients with indolent lymphoma without signs of active disease.

The stage of disease was defined according to the Ann Arbor staging system. Lymph nodes involved with lymphoma were considered bulky when found to have a maximum transverse diameter larger than 10 cm or, for thoracic masses, larger than 6 cm on a CT scan. EN lymphoma cases were defined by nodular or diffuse EN involvement excluding bone marrow and spleen involvement. Primary EN lymphoma (PENL) was defined as a lymphoma with a prevalent involvement of one or more EN site (i.e. stage I–IIE disease or stage IIIE–IV without bone marrow involvement and/or with minimal lymph node involvement).

Statistical analysis

Statistical analysis was performed using SPSS 12.0. All study comparisons were performed using the Fisher's exact test and all statistical tests were two-sided with a 5% level of significance.

Standardized incidence rates were calculated according to the world standard population [8] and also to the 2000 census population figures for the United States. Incidence trends were summarized by means of the annual percent change (APC) and joinpoint analysis was used to detect trend changes [9].

All patients received follow-up examinations up to December 31st 2006. Relative survival rates (RSR) were measured according to the Hakulinen method [10,11]. 'Period Analysis' techniques [12,13], based on the most recent available period, were used to estimate 5-year RSR for patients diagnosed in the period from 2002 to 2003. RSR for individual histological groups were compared using the Brown statistic [14].

Results

One thousand five hundred and eighty-two cases of PL were diagnosed in the province of Modena from 1997 to 2003. The frequencies of the analysed lymphoma subtypes are shown in Table 1.

Pattern of incidence and time trends

The World Age-Standardized Rates (ASR) varied substantially among lymphoid neoplasm subtypes. Overall, the ASR (per 100,000) was found to be 13.4, 2.2 and 3.4 for B-cell lymphomas, T-cell lymphomas and HL, respectively (Table 1). The overall APC of the World ASR was calculated at 1.62 (C.I. 95%: −4.32; 7.93) and no significant temporal points of trend change were detected using joinpoint analysis. In the present study no significant incidence trend was identified among the different histotypes.

Clinical data

The clinical characteristics of our patient cohort, according to lymphoma subtype, are summarized in Table 2. The

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Table 1. Absolute numbers, frequency and ASRs of PLs in the province of Modena (Italy)

PL subtype	ICD-O-3 codes	*N*	Freq. (all) %	Freq. (NHL) %	World ASR*			US ASR†
					M	F	Total	Total
B-cell lymphoma, all cases	9670–9699, 9761, 9823, 9940	1202	76	87.1	16.5	10.6	13.4	19.4
CLL/SLL	9670, 9823	327		23.7	4.5	2.3	3.3	5
LPC/WM	9671, 9761	116		8.4	1.4	0.9	1.1	1.7
HCL	9940	19		1.4	0.4	0.1	0.2	0.3
FL	9690–9698	150		10.9	2.1	1.8	2	2.6
MZL	9689, 9699	137		9.9	1.7	1.3	1.5	2.2
MCL	9673	40		2.9	0.6	0.3	0.4	0.6
DLBCL and BL	9675–9687	413		29.9	5.8	4	4.8	6.8
T/NK-cell lymphoma, all cases	9700–9719	178	11.3	12.9	3.1	1.5	2.2	3
MF/SS	9700, 9701	117		8.5	2.1	0.8	1.4	1.9
PTCL	9702–9708, 9716–9719	34		2.5	0.5	0.3	0.4	0.5
ALCL	9714	27		1.9	0.4	0.4	0.4	0.5
Hodgkin lymphoma, all cases	9650–9667	154	9.7	—	3.7	3.1	3.4	3.4
PL, NOS	9590–9596, 9709, 9760, 9827–9834, 9970	48	3	—	0.5	0.4	0.4	0.7
All cases		1582			23.8	15.6	19.4	26.5

ASR; age-standardized rates; M, male; F, female; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; LPC/WM, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia; HCL, hairy cell leukaemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large b-cell lymphoma; BL, Burkitt lymphoma; MF/SS, mycosis fungoides/ Sezary syndrome; PTCL, peripheral T-cell lymphoma; ALCL, anaplastic large cell lymphoma; NOS, not otherwise specified. Freq., frequency.
*According to the world standard population, per 100 000 person-years.
†According to the reported 2000 US population in 2000, per 100 000 person-years.

male to female ratio (M/F) for the whole population was 1.5 and the overall median age was 63 years (range 4–99 years). As shown in Figure 1, the incidence of disease was found to increase with age for each of the lymphoma subtype with the exception of HL, for which the classical bimodal distribution was observed. Interestingly a bimodal distribution of incidence according to age was observed also for males with MZL.

Forty-five percent of the cases had pure nodal disease and the bone marrow and spleen were involved in 44.5% and 11.2% of cases, respectively (656 and 177 cases). Splenic involvement was present in 8.5% of the HL (13 cases), 12.8% of the B-NHL (152 cases) and 5.1% of the T-NHL patients (9 cases). EN involvement was observed in 772 cases (49%) with 418 cases reclassified as PENL (26.4%). PENL was rare in HL (3.9%; six cases) and in SLL/CLL (3%; 10 cases). The EN sites involved in PENL by Lymphoma subtype are shown in Table 3.

Treatment data

Fifty-nine percent (928 cases) of the patients had received initial treatment within 3 months of their diagnosis. As expected, this frequency was higher for HL (136 cases, 97.8%) and aggressive NHL (415 cases, 86.6%) (data not shown). For patients with indolent NHLs including CLL, LPC, FL, MZL, HCL and MF, a watch and wait policy was adopted in 362 cases (47.6%) with the highest frequency in CLL/SLL (52%). Overall, 1115 (82.8%) patients received treatment that was considered adequate for their lymphoma. Moreover, 220 patients (16.3%) had been enrolled in a clinical trial. In comparing the group of younger versus elderly patients (cut off for age, 60 years) the frequency of patients treated with an adequate approach dropped from 94.9 to 76.1% ($p < 0.01$).

Survival data

After a median follow-up for living patients of 54 months (range 2–118), 741 had died and 841 remained alive, including 21 cases lost at follow-up. Overall, 82 patients died within 3 months of their diagnosis, accounting for an early death rate (EDR) of 5.2%. The EDR was higher for aggressive (48 cases, 10.5%) compared to indolent NHL (27 cases, 3.1%) and HL (2 cases, 1.3%) ($p < 0{,}001$) and also for elderly compared with younger patients (73 pz, 13.1% for age $\geq$65 vs. 9 pz, 5.4% for age <65; $p < 0.01$). In our current study population, the most frequent cause of death was found to be lymphoma progression (70.1% of deaths).

The 1, 3 and 5-year RSRs for all lymphoma cases were 81%, 73% and 70%, respectively. RSR for each lymphoma subtype is shown in Table 2. Period analysis was used to estimate the 5-year RSR values for patients with incomplete follow-up and to perform long-term comparisons of the RSR. An overall improvement in RSR was

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Table 2. Clinical features of all lymphoma cases under study by subtype*

	CLL/SLL	LPC/WM	HCL	FL	MZL	MCL	DLBCL/BL	MF/SS	PTCL	ALCL	HL
Number	327	116	19	150	137	40	413	117	34	27	154
M/F	1.42	1.52	2.8	0.92	1.04	1.86	1.17	2.65	1.46	1.07	1.17
Median age (Range)	69 (32–95)	71 (44–92)	60 (37–78)	59 (21–96)	64 (16–97)	67 (44–87)	64 (4–99)	64 (14–94)	63 (29–90)	57 (6–84)	42 (8–82)
PS %											
0–1	95.7	89.5	100	94.9	96.3	80	78	94.1	80.8	85.7	96
2-4	4.3	10.5	—	5.1	3.7	20	22	5.9	19.2	14.3	4
NA (%)	57.5	42.2	—	20.7	21.2	—	23.2	41.9	17.6	22.2	18.2
AA stage %											
I	0.7	7.6	—	23.9	43.1	15.4	31.4	90.6	17.9	24	9.7
II	1.1	0.9	—	14.8	10	2.6	18.8	2.6	17.9	36	59.7
III	0.4	—	—	17.6	1.5	5.1	11.9	2.6	21.4	8	16.7
IV	97.8	91.5	100	43.7	44.6	76.9	37.9	4.2	42.8	32	13.9
NA (%)	4	9.5	5.3	5.3	5.8	2.5	6.3	—	11.8	7.4	6.5
BM											
Positive	97.2	87.6	100	39.2	36	73.7	17.7	1.8	23.3	7.4	5.8
Negative	2.8	12.4	—	60.8	64	26.3	82.3	98.2	76.7	92.6	94.2
NA (%)	1.8	9.5	5.3	4.7	8.8	5	10.2	2.6	11.8	—	9.7
ENS %											
0	82.2	72.4	66.7	63.6	12.8	26.3	29	—	36.7	33.3	77
1	14	22.9	22.2	29.4	76.8	47.4	55.4	99.1	43.3	59.3	18
2+	3.8	4.7	11.1	7	10.4	26.3	15.6	0.9	20	7.4	5
NA (%)	1.8	9.5	5.3	4.7	8.8	5	9.9	2.6	11.8	—	9.7
B symptoms %	4.7	6.1	22.2	12.2	15	22.5	24.3	15.4	31.3	48.1	33.6
LDH > UNL %	15.1	18.5	12.5	23.4	15.9	28.1	52.5	31.3	61.1	41.2	18.3
NA (%)	45.2	44	15.8	28.7	35.8	20	28.8	86.3	47	37	18.2
5 year RSR %	83	74	100	80	76	38	44	97	31	65	86

*All percentage values are calculated from cases with no missing data.

M, male; F, female; PS, performance status; NA (#), not available (number); AA, Ann Arbor; BM, bone marrow; ENS, extranodal sites; LDH, lactate dehydrogenase; UNL, upper normal limit; SURV, survival; obs., observed; rel., relative; est., estimate; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; LPC/WM, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia; HCL, hairy cell leukaemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; MF/SS, mycosis fungoides/Sezary syndrome; PTCL, peripheral T-cell lymphoma; ALCL, anaplastic large cell lymphoma; HL, Hodgkin's lymphoma; RSR, relative survival rate.

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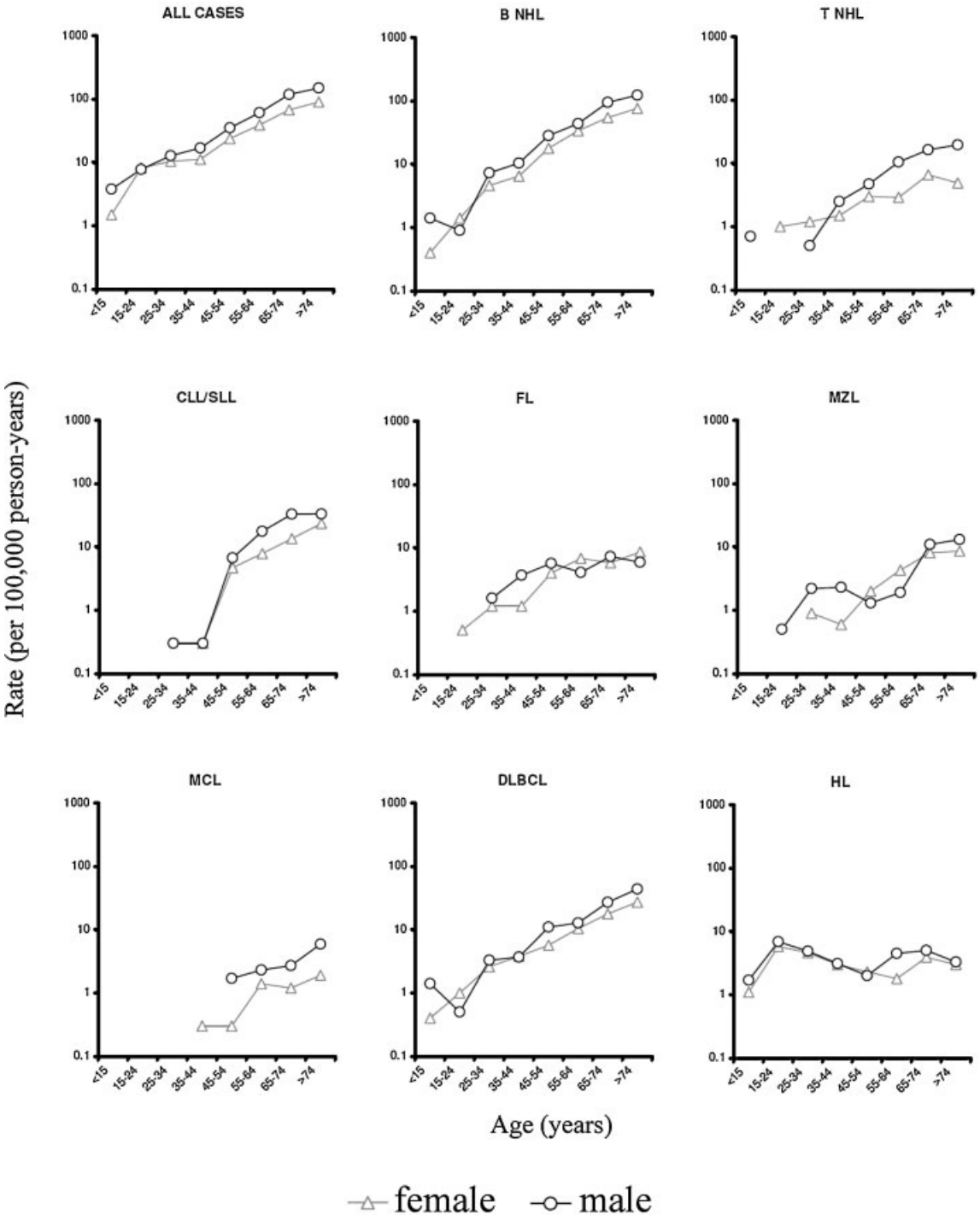

Figure 1. Incidence of lymphoid neoplasms by subtype, age and gender. CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma

observed over time with a 5-year RSR rising from 66% to 74% for cases diagnosed during 1997–2001 and 2002–2003, respectively ($p = 0.034$). A statistically significant improvement in the 5-year RSR for 2002–2003 patients was estimated for patients with diffuse large B-cell lymphoma (DLBCL) (from 41% to 54%; $p = 0.015$), HL (from 82% to 96%; $p = 0.004$) and T-NHL (from 73% to 87%; $p < 0.001$) (Figure 2).

Discussion

Our population-based study provides the first comprehensive analysis of the incidence patterns and trends for peripheral lymphoid neoplasms, classified according to the WHO guidelines, in the north Italian province of Modena. Additionally, we present the results of our detailed evaluation of the clinical features and outcomes from a

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Table 3. Primary extranodal sites excluding bone marrow and spleen

	CLL/SLL 10/327 (3%)*	LPC/WM 13/116 (11.2%)	MZL 73/137 (53.3%)	FL 23/150 (15.3%)	MCL 8/40 (20%)	DLBCL/BL 162/413 (39.2%)	MF/SS 105/117 (100%)	PTCL 8/34 (23.5%)	ALCL 10/27 (37%)	HL 6/154 (3.9%)
Pharynx/larynx	—	1 (7.7)**	1 (1.4)	6 (26.1)	2 (25)	15 (9.2)	—	—	2 (20)	1 (16.7)
Salivary and lacrimal glands	1 (10)	2 (15.4)	8 (11)	5 (21.7)	—	3 (1.9)	—	—	—	1 (16.7)
Lung	—	1 (7.7)	2 (2.7)	—	—	5 (3.1)	—	1 (12.5)	—	1 (16.7)
Stomach, GI tract	—	1 (7.7)	32 (43.8)	1 (4.3)	—	46 (28.4)	—	3 (37.5)	1 (10)	—
Liver	2 (20)	—	1 (1.4)	—	1 (12.5)	3 (1.9)	—	—	—	1 (16.7)
Urogenital tract	—	—	—	1 (4.3)	—	7 (4.3)	—	—	—	—
CNS	—	—	—	—	—	18 (11.1)	—	—	—	—
Skin	—	1 (7.7)	16 (21.9)	6 (26.1)	—	11 (6.8)	105 (100)	2 (25)	5 (50)	—
Bone	1 (10)	2 (15.4)	1 (1.4)	1 (4.3)	—	6 (3.7)	—	—	1 (10)	—
Other sites	1 (10)	—	2 (2.7)	—	—	5 (3.1)	—	—	—	1 (16.7)
Multiple ENS	5 (50)	5 (38.4)	10 (13.7)	3 (13.2)	5 (62.5)	43 (26.5)	—	2 (25)	1 (10)	1 (16.7)

*Proportion of PENL cases on all cases by Lymphoma subtype.
**proportion of single EN site on PENL cases by Lymphoma subtype.
GI, gastrointestinal; CNS, central nervous system; ENS, extranodal sites; HL, Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; LPC/WM, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; MF/SS, mycosis fungoides/Sezary syndrome; PTCL, peripheral T-cell lymphoma; ALCL, anaplastic large cell lymphoma.

large unselected series of lymphoid neoplasms. The aim of our study, however, was not only to provide pure epidemiological data on malignant lymphomas, but also to use a population-based approach to provide more detailed and clinically useful information regarding the histological and clinical features of a well-characterized series of patients with lymphoma. Based on the excellent coverage of the MCR, documented by a very low rate of DCO cases (death certificate only; <0.1%) [6] the quality of our data should be considered very high.

Differing from other available epidemiological reports, we decided to include clinical entities as defined by the WHO classification system [1]. For this reason, both small lymphocytic lymphoma and its leukaemic counterpart, CLL, were classified as one histological group. Moreover, according to recently defined diagnostic criteria [1,15], we decided to include in the group of lymphoplasmacytoid lymphomas, all cases with a serum IgM monoclonal component and a clonal lymphoplasmacytic bone marrow infiltrate. We believe that this strategy makes our results more useful to clinicians, as they describe different clinical entities as they are actually managed in daily clinical practice. It should be noted, however, that for some lymphoma subtypes our findings could incorrectly suggest large differences in the frequency and incidence compared with the existing published epidemiological data.

The calculated world ASR for all malignant lymphomas of our series is 15.6 cases per 100,000 people (19.6 and 12.1 for males and females, respectively, Table 1). 'Cancer in five continents (1992–1997)' data were used to compare our present results with those available from other countries. Keeping in mind all possible biases when performing comparisons of incidence data (time frame, disease grouping, quality of data reporting), we found that the NHL and HL incidence in the Modena population was amongst the highest observed in any western industrialized country. In particular, when evaluating other European countries, our data seem to confirm a high incidence of both NHL and HL in Italy, which is close to the reported incidences of this disease in other south European countries including Spain, France and southern regions of Switzerland [16]. More recent data describing the incidence of malignant lymphomas diagnosed over a similar period of time and disease categorization to that used in our present study were recently published by the US-SEER Cancer Registry [17]. In order to compare our results with these data from the United States, the ASRs in the US population were calculated; the incidence of NHLs in Modena was found to be slightly higher than that observed over a similar time frame in the US population (22.4 vs. 20.5).

When evaluating single lymphoma subtypes, we made some novel observations. Apart from the DLBCL cases that were confirmed as the most frequent lymphoma subtype (29.9% of all NHLs, ASR 4.8 cases/100,000), we observed very high incidence of indolent lymphomas (54%, ASR 9.5). CLL/SLL was found to be the second lymphoma subtype both in terms of frequency (23.7% of NHL) and of incidence (ASR = 3.3). FL represented the third lymphoma subtype (10.9%, ASR = 2.0) and only

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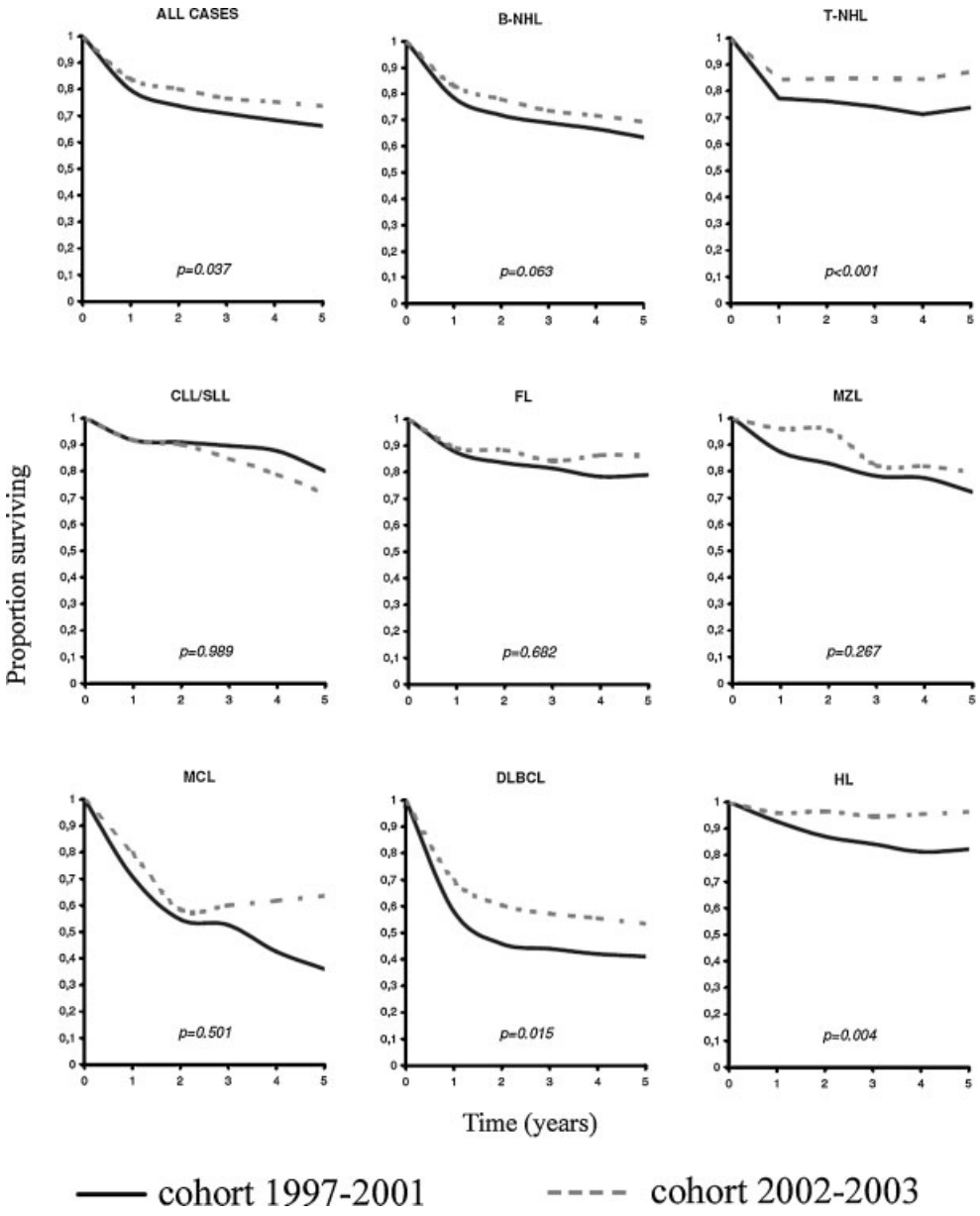

Figure 2. Relative survival by lymphoma subtype and period of diagnosis (1997–2001 vs. 2002–2003). CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma

slightly lower incidences were observed for MZL (9.9%, ASR = 1.5) and LPC/WM (8.47, ASR = 1.1). Low-grade lymphomas have been previously reported to have a lower frequency, around 30% [18,19], and we think that this difference is mainly due to the use of different classification systems, such as the exclusion of classic CLL in older studies as previously mentioned. Moreover referral of indolent lymphoma cases to cancer registries could have been reduced in some old series as a consequence of the low rate of hospital admissions and of the high rate of patients with low-grade NHL not requiring therapy as documented also by our results. More recent studies that evaluated patient data over a similar time frame in both the United States and Europe, seem to confirm our findings of high rates of indolent lymphomas but also suggest differences of the rate of single low-grade lymphoma subtypes [17,20]. Both the incidence and frequency of MZL that we have calculated (ASR = 2.2; 9.9% of cases) are higher when compared with reports from either the United States or other European countries [17,20]. Comparing our results with those available from the US we also showed a higher incidence of MF/SS (1.9 vs. 0.5) and lower rates of FL cases (2.6 vs. 3.2) confirming, for this Lymphoma subtype, previous observations [2,19]. Also if differences in the reclassification of cases could have biased the results, our study confirms that differences in the epidemiology and world distribution of lymphomas exist; these could be explained both by differences in the ethnicity of the studied populations and by different exposures to known and unknown risk factors; for example high incidence observed for MZL could be partly associated to the high prevalence of known etiological factors such as HCV infection reported in Italy and South Europe [21,22].

In terms of time trends of incidence, our current data demonstrated only a slight increase in the incidence of PL

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(1.62% per year). This is very consistent with the incidence reported from other case series and confirms that there has been a marked decrease in incidence change in recent years in other countries [5,16,17]. Unfortunately, we were unable to provide incidence trends for single lymphoma entities, probably due to the low number of cases and to the relatively short period of observation.

The clinical characteristics of PL examined in our study do not markedly differ from the data reported in other European studies [23–27]. We contend, however, that our present data have a higher level of accuracy because they were determined by active chart review.

An important objective of our study was to assess patients' outcome; our data confirm that there has been an overall improvement in outcome when compared with available historical controls from other European countries [28,29]. An interesting finding that arises from our analysis of the 5-year RSR is that for some lymphoma subtypes, including HCL and MF/SS, the impact of the diagnosis on life expectancy was null or minimal, as evidenced by 5-year RSR of 100% and 97%, respectively. This finding is particularly relevant if one looks at the relatively young median age of patients with either HCL or MF/SS (60 and 64 years, respectively). In addition, by using 'Period Analysis', which is considered to be a strong statistical tool for estimating longer survival data for patients with a relative short median follow-up, we also demonstrate an improvement in survival within our present study period that is statistically significant for all cases and for single lymphoma entities including DLBCL, T-NHL and HL (Figure 2). The 5-year RSR improvement estimated for both T-NHL and HL could be explained by the better use of existing drugs or different combinations of these agents, or by the use of more accurate diagnostic and/or prognostic tools. In addition, for cases of T-NHL, the greatest 5-year RSR improvement was measured for MF and not for aggressive PTCL, thus suggesting that better survival can probably be explained also by a high number of patients diagnosed with an indolent disease in more recent years. Interestingly, the survival improvement that we observe for DLBCL cases confirms the findings of a recent population-based study of DLBCL in Canada [30] and can be explained mainly by the increased use of more effective drugs such as anti-CD20 monoclonal antibodies, and to a minor extent by the use of more accurate diagnostic and/or prognostic tools. The effects of the use of anti-CD20 monoclonal antibodies and of more accurate diagnostic approaches will probably have an impact in survival of other B-cell lymphomas also, such as FL. However, as FL are indolent neoplasms with a prolonged median OS, the limited follow-up information in our study allowed us to demonstrate only a trend toward a better outcome for more recent cases.

In conclusion, we believe that by providing a comprehensive description of all lymphoma cases in the province of Modena, we have made a contribution towards an increased understanding of this disease both in terms of incidence, clinical features and patient outcome. Our results show that there is a relatively homogeneous distribution of lymphoma subtypes in northern Italy in comparison with that reported in other western countries, with the only exception being the higher rates of indolent lymphomas and of MZL. We also demonstrate that some lymphoma subtypes (MF/SS and HCL) have a minimal or null impact on life expectancy and that there has been an overall survival improvement for most patients with malignant lymphoma.

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