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Population-based incidence of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain

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ABSTRACT

Background: The aim of this study was to describe incidence patterns of lymphoid neoplasms in the Girona province (Spain) (1996–2015), and to predict the number of cases in Spain during 2020.
Methods: Data were extracted from the Girona cancer registry. Incident cases were classified using the ICD-O-3, third revision, and grouped according to the WHO 2008 classification scheme. Age-adjusted incidence rates to the European standard population (ASRE) were estimated and incidence trends were modeled using Joinpoint.
Results: 4367 lymphoid neoplasms were diagnosed in the Girona province. The ASRE for overall lymphoma was 37.1 (95% CI: 36.0; 38.2), with a marked male predominance in almost all subtypes. During 1996–2015, incidence trends remained stable for broader lymphoma categories. According to our predictions, 17,950 new cases of LNs will be diagnosed in Spain in 2020.
Conclusions: This 'real-world' data will provide valuable information to better inform etiological hypotheses and plan future health-care services.

1. Introduction

Lymphoid neoplasms (LNs) are a heterogeneous group of hematological malignancies presenting diverse etiology, presentation and outcomes [1]. Changing classification schemes [i.e. the Working Formulation (WF-1982), the Revised European-American Lymphoma (REAL, 1994) and the World Health Organization (WHO, 2001, 2008 and 2016) classifications] and scarcity of subtype-specific epidemiological data hamper international comparisons. The aim of this study was to describe incidence patterns of LNs in the Girona province (Spain) (1996–2015) according to the WHO 2008 classification, and to predict the number of LNs in Spain during 2020.

2. Material and methods

Data were extracted from the population-based Girona cancer registry, covering a population of 738,976 inhabitants in 2015. Incident cases were registered using the International Classification of Diseases for Oncology, third edition (ICD-O-3) and grouped according to the WHO 2008 classification scheme. Age-adjusted incidence rates to the European standard population (ASRE) were estimated and Joinpoint regression modeling was used to examine temporal trends in age-standardized rates. Sex- and age-specific projections of cases in Spain in 2020 were estimated, based on the *National Statistics Institute of Spain* projections of population.

Abbreviations: ASRE, age-adjusted incidence rate to the European population; APC, annual percent change; ICD-O-3, International Classification of Diseases for Oncology, third edition; LN, lymphoid neoplasm; WHO, World Health Organization

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Table 1
Lymphoid neoplasms incidence rates by subtype in Girona, Spain (1996–2015).

Subtype	ICD-O-3 codes	N	%	Annual N	Median age (years)	CR	ASR_{E13} (CI 95%)	Sex ratio[1]
Lymphoid neoplasm, total		**4367**	**100.00**	**218**	**67.6**	**33.42**	**37.08 (35.98; 38.21)**	**1.54**
1) Hodgkin lymphoma		**364**	**8.34**	**18**	**39.7**	**2.79**	**2.72 (2.44; 3.02)**	**1.59**
1.1 Classical Hodgkin lymphoma		336	92.31	17	39.1	2.57	2.50 (2.24; 2.79)	1.55
1.1.1 Lymphocyte-rich classical Hodgkin lymphoma	9651	21	6.25	1	34.4	0.16	0.15 (0.09; 0.23)	6.25
1.1.2 Nodular sclerosis classical Hodgkin lymphoma	9663-9667	214	63.69	11	36.7	1.64	1.56 (1.36; 1.79)	1.13
1.1.3 Mixed cellularity classical Hodgkin lymphoma	9652	66	19.64	3	46.4	0.51	0.51 (0.39; 0.65)	2.57
1.1.4 Lymphocyte-depleted classical Hodgkin lymphoma	9653-9655	5	1.49	0	52.5	0.04	0.04 (0.01; 0.09)	NA
1.1.5 Classical Hodgkin lymphoma, NOS	9650,9661-9662	30	8.93	2	53.3	0.23	0.24 (0.16; 0.35)	2.06
1.2 Nodular lymphocyte predominant Hodgkin lymphoma	9659	28	7.69	1	43.8	0.21	0.22 (0.15; 0.32)	2.07
Non-Hodgkin lymphoma		**3886**	**88.99**	**194**	**68.6**	**29.74**	**33.35 (32.3; 34.42)**	**1.54**
2) Precursor lymphoid neoplasms		**210**	**4.81**	**10**	**25**	**1.61**	**1.64 (1.42; 1.88)**	**1.53**
2.1 B-lymphoblastic leukemia/lymphoma	9728, 9811-9818, 9836	138	65.71	7	18.2	1.06	1.08 (0.91; 1.28)	1.25
2.2 T-lymphoblastic leukemia/lymphoma	9729, 9837	46	21.90	2	20	0.35	0.34 (0.25; 0.46)	3.53
2.3 Lymphoblastic leukemia/lymphoma, NOS	9727, 9835	26	12.38	1	80	0.20	0.22 (0.14; 0.32)	1.37
3) Mature B-cell neoplasms		**3413**	**78.15**	**171**	**69.7**	**26.12**	**29.5 (28.51; 30.51)**	**1.48**
3.1 Chronic lymphocytic leukemia/small lymphocytic lymphoma	9670, 9823	751	22.00	38	72.4	5.75	6.62 (6.15; 7.11)	1.77
3.2 B-cell prolymphocytic leukemia	9833	–	–	–	–	–	–	–
3.3 Mantle cell lymphoma	9673	105	3.08	5	68.1	0.80	0.92 (0.75; 1.12)	4.37
3.4 Lymphoplasmacytic lymphoma/ Waldenström's Macroglobulinemia	9671, 9761	128	3.75	6	73.5	0.98	1.13 (0.94; 1.34)	2.16
3.5 Diffuse large B-cell lymphoma	9678-9680,9688, 9684, 9712, 9735, 9737,9738	733	21.48	37	66.3	5.61	6.18 (5.74; 6.65)	1.4
3.6 Burkitt lymphoma/leukemia	9687, 9826	60	1.76	3	37.9	0.46	0.47 (0.36; 0.61)	1.91
3.7 Marginal lymphoma		339	9.93	17	68.7	2.59	2.92 (2.62; 3.25)	1.09
3.7.1 Splenic marginal zone lymphoma	9689	67	19.76	3	69.2	0.51	0.58 (0.45; 0.74)	1.46
3.7.2 Extranodal marginal zone lymphoma	9699 (excluding C77.0-C77.9)	243	71.68	12	68	1.86	2.09 (1.83; 2.37)	1.07
3.7.3 Nodal marginal zone lymphoma	9699 (C77.0-C77.9)	29	8.55	1	75.8	0.22	0.25 (0.17; 0.36)	0.60
3.8 Follicular lymphoma	9597, 9690, 9691, 9695, 9698	441	12.92	22	62.1	3.37	3.74 (3.4; 4.11)	1.07
3.9 Hairy cell leukemia	9940	32	0.94	2	58.8	0.24	0.26 (0.18; 0.37)	6.86
3.10 Plasma cell neoplasms		820	24.03	41	72.7	6.27	7.22 (6.73; 7.73)	1.41
3.10.1 Solitary plasmocytoma of bone	9731	36	4.39	2	69	0.28	0.31 (0.22; 0.43)	2.10
3.10.2 Extraosseus plasmocytoma	9734	13	1.59	1	76.9	0.10	0.12 (0.07; 0.2)	2.25
3.10.3 Plasma cell myeloma/leukemia	9732-9733	771	94.02	39	72.8	5.90	6.79 (6.32; 7.29)	1.38
3.11 Heavy chain disease	9762	–	–	–	–	–	–	–
3. 12 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL	9596	4	0.12	0	44.5	0.03	0.03 (0.01; 0.08)	1.33
4) Mature-T-cell and NK-cell neoplasms		**263**	**6.02**	**13**	**64.7**	**2.01**	**2.22 (1.96; 2.51)**	**2.59**
4.1 Mycosis fungoides/Sezary syndrome	9700, 9701	81	30.80	4	64.2	0.62	0.69 (0.55; 0.86)	2.78
4.2 Peripheral T/NK-cell lymphoma		130	49.43	6	60.50	0.99	1.08 (0.91; 1.30)	2.95
4.2.1 Peripheral T-cell lymphoma, NOS	9702	60	46.15	3	64.2	0.46	0.5 (0.38; 0.65)	2.52
4.2.2 Angioimmunoblastic T-cell lymphoma	9705	29	22.31	1	70.6	0.22	0.26 (0.17; 0.37)	3.23
4.2.3 Subcutaneous panniculitis-like T-cell lymphoma	9708	2	1.54	0	42	0.02	0.01 (0.00; 0.05)	0
4.2.4 Anaplastic large cell lymphoma, ALK-positive	9714	18	13.85	1	37	0.14	0.14 (0.08; 0.22)	8.33
4.2.5 Hepatosplenic T-cell lymphoma	9716	3	2.31	0	42.5	0.02	0.02 (0.00; 0.07)	NA
4.2.6 Enteropathy-associated T-cell lymphoma	9717	1	0.77	0	62.5	0.01	0.01 (0.00; 0.05)	0
4.2.7 Primary cutaneous gamma-delta T-cell lymphoma	9726	–	–	–	–	–	–	–
4.2.8 Primary cutaneous T-cell lymphoma, NOS	9709	16	12.31	1	73	0.12	0.13 (0.07; 0.22)	3.14
4.2.9 Systemic EBV-positive T-cell lymphoproliferative disease of childhood	9724	–	–	–	–	–	–	–
4.2.10 Hydroa vacciniforme-like lymphoma	9725	1	0.77	0	17.5	0.01	0.01 (0.00; 0.05)	NA
4.3 Adult T-cell leukemia/lymphoma	9827	3	1.14	0	82.5	0.02	0.02 (0.00; 0.07)	0.67
4.4 Extranodal NK/Tcell lymphoma, nasal type	9719	11	4.18	1	66.2	0.08	0.09 (0.04; 0.17)	1.86
4.5 T-cell large granular lymphocytic leukemia	9831	22	8.37	1	65	0.17	0.19 (0.12; 0.29)	2.25
4.6 T-cell prolymphocytic leukemia	9834	3	1.14	0	62.5	0.02	0.03 (0.01; 0.08)	0
4.7 Aggressive NK cell leukemia	9948	1	0.38	0	22.5	0.01	0.01 (0.00; 0.05)	NA
4.8 Primary cutaneous CD30 + T-cell lymphoproliferative disorders	9718	12	4.56	1	70	0.09	0.10 (0.05; 0.18)	2.33

(*continued on next page*)

Table 1 (*continued*)

Subtype	ICD-O-3 codes	N	%	Annual N	Median age (years)	CR	ASR_{E13} (CI 95%)	Sex ratio[1]
5) Lymphoid neoplasms, NOS	**9590, 9591, 9820, 9970, 9971**	**117**	**2.68**	**6**	**77.9**	**0.90**	**1.01 (0.83; 1.21)**	**1.42**

N, total cases; CR, crude rate; ASRE, age-standardized incidence rate using European 2013 standard population.
[1]Sex ratio (M/F) based on ASRE.

Table 2
Trends in lymphoid neoplasms incidence rates by major subtypes in Girona, Spain (1996–2015).

	Period	APC	CI 95%
Lymphoid neoplasms	1996-2015	0.1	(-0.6; 0.8)
Hodgkin lymphoma	1996-2015	0.7	(-1.4; 2.9)
Precursor lymphoid neoplasms	1996-2015	−1.5	(-4.1; 1.2)
Mature B-cell neoplasms	1996-2015	0.3	(-0.5; 1.2)
Chronic lymphocytic leukemia/small lymphocytic lymphoma	1996-2015	−0.1	(-1.4; 1.3)
Mantle cell lymphoma	1996-2015	1.8	(-2.8; 6.6)
Lymphoplasmacytic lymphoma/ Waldenström's macroglobulinemia	1996-2015	1.2	(-1.3; 3.9)
Diffuse large B-cell lymphoma	1996-2015	0.5	(-1.1; 2.0)
Burkitt lymphoma/leukemia	1996-2015	−3.3	(-7.9; 1.6)
Marginal lymphoma	1996-2015	0.4	(-0.9; 1.7)
Follicular lymphoma	1996-2015	1.2	(-1.2; 3.6)
Plasma cell neoplasms	1996-2015	0.3	(-1.4; 1.9)
Mature T-cell and NK-cell neoplasmns	1996-2015	1.7	(-1.9; 5.6)
Lymphoid neoplasms, NOS	1996-2015	−7.4*	(-11.2; -3.3)

APC, annual percent change; NOS, not otherwise specified.
Calculated only for major lymphoma categories and most incident mature B-cell neoplasms.
* p-value < 0.05.

3. Results

4367 LNs incident cases (59.7% men) were diagnosed in the Girona province. Among them, 364 (8.3%) were Hodgkin-lymphoma, 210 (4.8%) precursor lymphoid neoplasms, 3413 (78.2%) mature B-cell neoplasms, 263 (6.0%) mature T-cell and NK-cell neoplasms, and 117 (2.7%) lymphoid neoplasms not otherwise specified (NOS). Detailed information can be found in Table 1. In brief, the median age at diagnosis ranged from 25 to 77.9 years according to the major LNs subtypes. Overall in both sexes, the top five most frequent entities were: plasma cell neoplasm (820), chronic lymphocytic leukemia/small lymphocytic lymphoma (751), diffuse large B-cell lymphoma (733), follicular lymphoma (441) and marginal lymphoma (339). The LNs crude rate (CR) was 33.4 and ASRE was 37.1 (95% confidence interval (CI): 36.0; 38.2), 45.7 (95% CI: 43.9; 47.6) in men and 29.7 (95% CI: 28.4; 31.1) in women. There was a marked male predominance; the incidence sex ratio (male/female) ranged from 1.1 for follicular and marginal lymphomas to 6.9 for hairy cell leukemia.

During 1996–2015, no statistically significant variations in incidence trends were found for LNs [annual percentage change (APC): 0.1 (95% CI: −0.6; 0.8)], nor for broader lymphoma categories (Table 2). Only the LNs NOS subtype category decreased, evidencing the improved diagnostic specificity for these malignancies during the last years.

According to our predictions, 17,950 new cases of LNs will be diagnosed in Spain in 2020, of which 1264 cases will be Hodgkin lymphoma, 738 precursor lymphoid neoplasms, 14,361 mature B-cell neoplasms (i.e. 3248 chronic lymphocytic leukemia/small lymphocytic lymphoma, 445 mantle cell lymphoma, 544 lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, 3025 diffuse large B-cell lymphoma, 221 Burkitt lymphoma/leukemia, 1394 marginal lymphoma, 1811 follicular lymphoma, 129 hairy cell leukemia, and 3531 plasma cell neoplasms), 1067 mature T-cell and NK-cell neoplasms and 521 LNs NOS (*data not shown*).

4. Discussion

This paper presents epidemiological data of LNs in the province of Girona (Spain) during a 20-year period. Incidence rates for the most frequent subtypes were in accordance with those reported in France (1980–2009) [2], United Kingdom (2004–2014) [3], Europe (2000–2002) [4], and generally lower in comparison to those from the

United States (projected incidence in 2016) [5] or Australia (1982–2006) [6]. Regarding specific entities, we reported higher rates of mantel cell lymphoma (ASRE = 0.92), to the date only linked to few genetic and environmental risk factors (i.e. atopy, allergy or farm life) [7], which merit further research. In the same vein, Burkitt lymphoma/leukemia incidence (ASRE = 0.47) was particularly high in our region, a pattern largely reported in other Southern European regions, yet unexplained by well-stablished etiological factors [8]. Similarly, we reported higher rates of chronic lymphocytic leukemia/small lymphocytic lymphoma (ASRE = 6.62), mainly attributable to a higher completeness of our cancer registry for this entity rather than to a real peak of incidence in our region. Chronic lymphocytic leukemia – as well as Waldenström's macroglobulinemia – have been shown to be underreported by cancer registries given that they are prone to be indolent and their diagnosis is not based on tissue pathology [9]. To ensure a complete coverage of all chronic lymphocytic leukemia cases in our region, we recently performed review of alternative sources of information (e.g. flow cytometry and hematologists databases) and evidenced a 18.2% of underreported cases during 1998–2013 [10]. Non-specialized cancer registries thus, should make additional efforts to ensure the surveillance of these malignancies is entirely accurate.

Incidence trends are broadly consistent with those reported for other Western countries, which describe a steady increase in the incidence of LNs during the 80′s and a stabilization in the late 90′s [5,6,11]. Furthermore, in the United States, even a slight decline in incidence rates by 2000 has been reported [5], which has been widely related to a decrease in AIDS incidence, but also suggested to reflect coding changes in 2001, when the WHO classification system was first published [12]. Despite concordance between ICD-O-3, which incorporates the WHO Classification, and cases originally diagnosed and coded under previous systems is generally high [13], several changes can be rarely overcame. For example, the 2008 International Workshop on chronic lymphocytic leukemia, changed the definition of the disease by requiring an absolute B-cell count of 5000 cells/μL rather than the previous absolute lymphocyte count of 5000 cells/μL, causing many former Rai stage 0 cases to be reclassified as monoclonal B-cell lymphocytosis, a pre-malignant disorder not recorded by cancer registries [14]. Overall, our results have to be interpreted cautiously since the numerous changes in the classification of LNs over time could result in errors of diagnosis or coding translation, particularly during the earlier period.

The number of expected lymphoma cases depicts accurately the cancer burden of LNs in Spain, which lacks of a cancer registry with national coverage, but data on specific subtypes should be interpreted with caution. Some WHO LNs subtypes are extremely rare, making estimates less robust. However, overall, these results are interesting for clinicians and public health in evaluating the cost of management and new treatments for these pathologies.

In 2016, a new WHO manual was released [15] but the available surveillance data are through 1996–2015 and do not reflect these updates. The capability of registries to recode previous cases to these new schemes will be limited because many require additional molecular or clinical data [5]. However, changes to the 2008 classification are relatively small and would not be expected to change our conclusions. The impact of these changes will be unclear until next years, when they become adopted by pathologists and new entities routinely distinguished in clinical practice.

5. Conclusions

In conclusion, this study describes in detail the incidence of LNs categorized by 2008 WHO subtype in a large population-based cohort. This has not been performed previously for Spain, and complements the subtype-specific analyses published for Europe [2–4], the United States [5], and Australia [6]. This ‘real-world’ data will provide valuable information to better inform etiological hypotheses and plan future health-care services.

Author contribution

- Study conception and design: RMG, MSo
- Acquisition of data: RMG, AF, IG, JMR, AB, NK, JB
- Analysis of data: AF, DM
- Interpretation of data: MSo, RMG, AF, DM, CA, MSa
- Manuscript writing: MSo
- Critical review of the article and final approval of the article: all authors

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Conflict of interest

None.

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