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Review Article

Epidemiology of malignant lymphomas in Italy

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Abstract

Malignant lymphomas are the commonest hematological cancers, accounting for about 50% of them. Despite being diagnosed worldwide, differences have been reported in terms of absolute incidence in different geographical areas, being more frequently seen in Europe and Northern America rather than Asia and Africa. Even more evident is the different distribution of lymphoma types, based on the presence of different causative agents (e.g., HTLV1), postulated genetic backgrounds (eg. EBV-associated T-cell neoplasms), or unknown reasons. In this study, we aimed to assess, for the first time, the specific incidence of lymphoma types in Italy. To this aim, we included in the analysis 2,952 cases, collected in different regions, covering North, Center, and South of Italy, over a three-year period. We found that diffuse large B-cell lymphomas and follicular lymphomas are the commonest types, while T-cell lymphomas are overall rare. Interestingly, chronic lymphocytic leukemia/small lymphocytic lymphoma was diagnosed more often in the South. Differently from current literature, we found angioimmunoblastic lymphoma to be commoner in women, while anaplastic large cell lymphoma was recorded more frequently in men. Our findings were then discussed in the light of other available regional reports from Asia, Africa, Europe, and Americas. In conclusion, we provided for the first time to the best of our knowledge a description of relative incidence of lymphoma types in Italy, posing the rational basis for ad hoc analyses on risk factors and possible clinical strategies.

Introduction

Malignant lymphomas represent approximately 4-6% of new cancers each year worldwide. However, their incidence is quite variable across the Globe (Figure 1). In fact, they are more common in Western countries, especially USA and Europe. A survey run by the Surveillance Epidemiology and End Results (SEER) program indicates an incidence rate of 19.6 cases of non-Hodgkin lymphomas (NHL) and 2.6 cases of Hodgkin lymphoma (HL) per 100,000 persons per year, with a mortality rate of 5.3 and 0.3 per

100,000 persons per year, respectively, in United States [1]. Overall, the lifetime risk of developing these diseases is approximately 2.1% for NHL and 0.2% for HL, based on 2016-2018 data [1]. By contrast, the European Cancer Observatory (ECO), a project developed by the International Agency for Research on Cancer (IARC), estimates an incidence in Europe of 16.4 NHL and 2.7 HL cases/100,000/year in 2020 [2]. As far as Italy is concerned, 22.6 new NHL cases/100,000/year (corresponding to 14,032 new cases in 2020) and 3.4 HL cases/100,000/year (2,120 new cases in 2020) were diagnosed [2]. Overall, lymphomas constituted about 4% of all cancers in Italy. When all the other hematologic malignancies are considered (therefore also including multiple myeloma, leukemias, myelodysplastic syndromes and chronic myeloproliferative neoplasms), the whole group of hemato-lymphoid tumors constituted 8.16% of all cancers, with 31,256 new diagnoses in 2020 [2]. The lowest incidence of lymphomas worldwide is described in most Asian and Africa countries [3] (Figure 1). Detailed data on lymphoma incidence in USA, Europe and Italy are presented in Table 1 Of interest, differently from what observed in USA and northern Europe, where the incidence of NHL has progressively raised in the last two decades (HL remaining stable), the incidence of both HL and NHL did not significantly vary over time in Italy (Figure 2A-C). Beside general estimation on NHL and HL, more detailed reports on NHL subtypes in single geographical areas are definitely scant (4,5). Particularly, no systematic descriptive analysis has considered incidence of lymphoid neoplasm subtypes as defined by the WHO classification in Italy. Bearing this in mind, in the present study we aimed to assess the relative incidence of lymphoma subtypes as defined by the 2017 WHO classification in Italy.

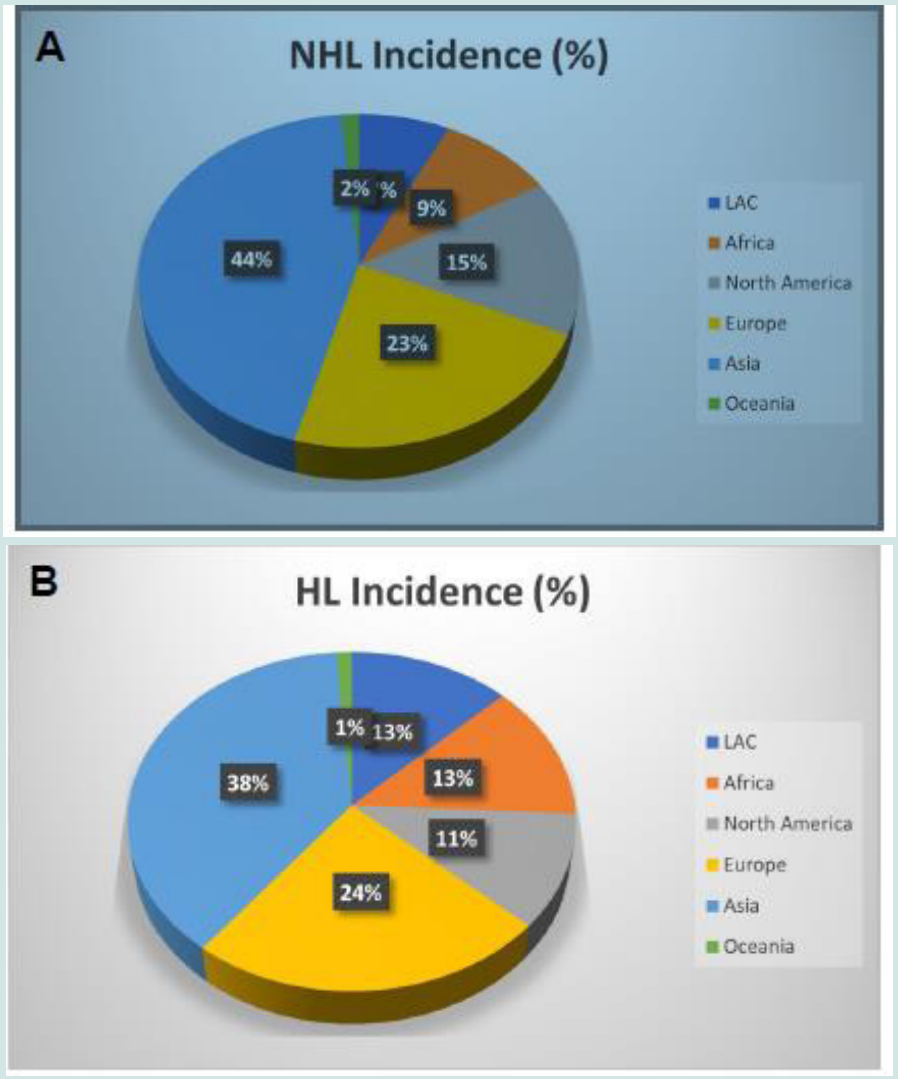
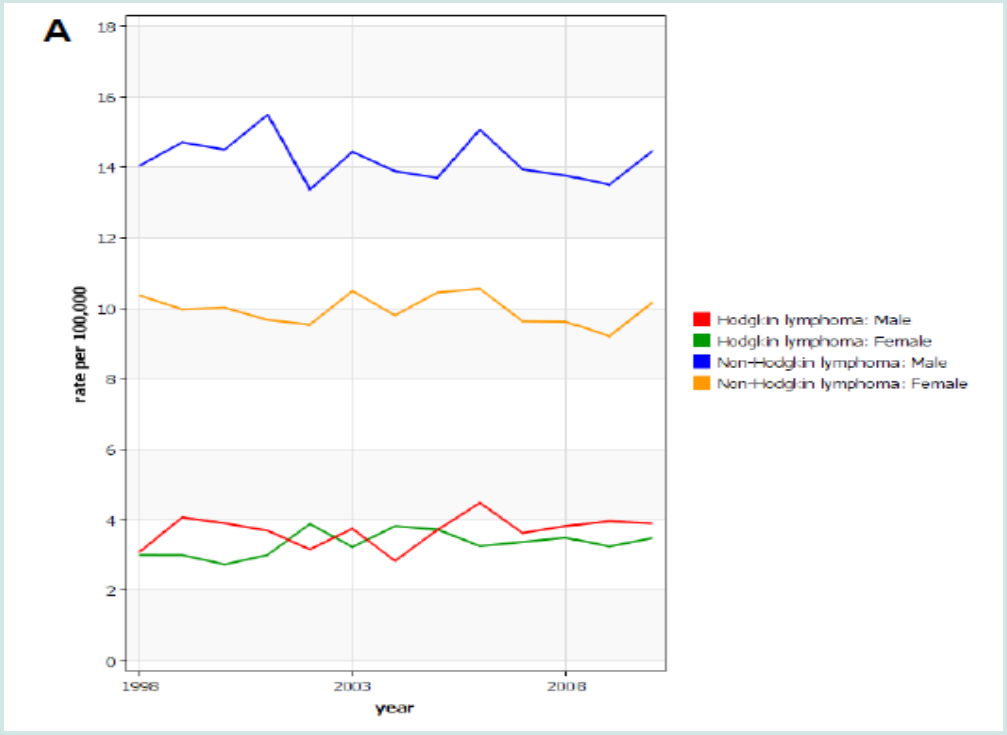


Figure 1: A) Distribution of non-Hodgkin lymphoma cases worldwide. Source Global Cancer Observatory (IARC); LAC= Latin America and Caribbean. Adapted from IARC, Cancer Totay. B) Distribution of Hodgkinlymphoma cases worldwide. Source Global Cancer Observatory (IARC); LAC= Latin America and Caribbean. Adapted from IARC, Cancer Totay.


A
rate per 100,000
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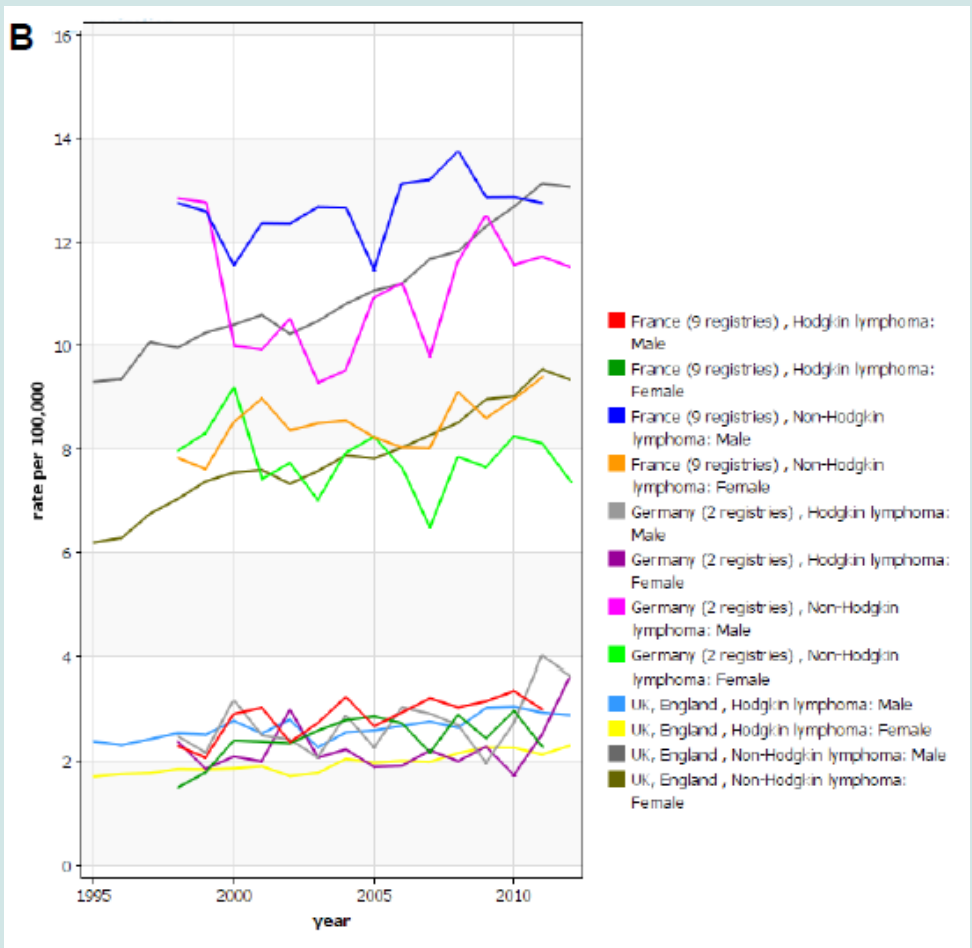
1998
2003
2008
Hodgkin lymphoma: Male
Hodgkin lymphoma: Female
Non-Hodgkin lymphoma: Male
Non-Hodgkin lymphoma: Female


B
rate per 100,000
year
1995
2000
2005
2010
France (9 registries) , Hodgkin lymphoma: Male
France (9 registries) , Hodgkin lymphoma: Female
France (9 registries) , Non-Hodgkin lymphoma: Male
France (9 registries) , Non-Hodgkin lymphoma: Female
Germany (2 registries) , Hodgkin lymphoma: Male
Germany (2 registries) , Hodgkin lymphoma: Female
Germany (2 registries) , Non-Hodgkin lymphoma: Male
Germany (2 registries) , Non-Hodgkin lymphoma: Female
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UK, England , Non-Hodgkin lymphoma: Female

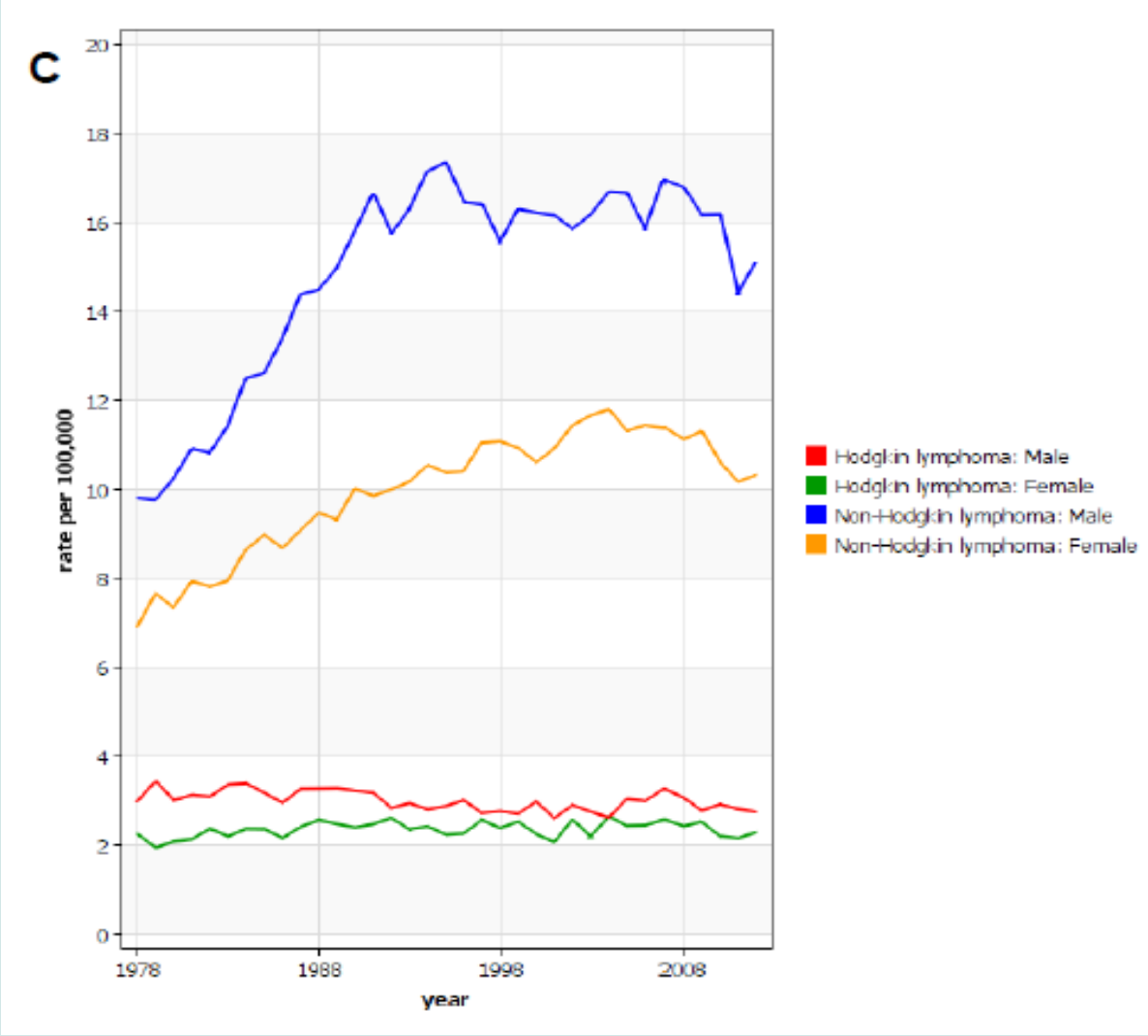


Figure 2: Age standardized incidence rate of malignant lymphomas in Italy between 1998 and 2010 in Italy (A), Europe (data from Germany, France and UK)(B), and USA (SEER, 9 registries) (C). Source Global Cancer Observatory (IARC).

Table 1: Incidence of malignant lymphomas in Europe, USA, and Italy.

	Non-Hodgkin lymphomas	Hodgkin lymphomas	Total
Number of new cases*			
USA	80,470	8,540	89,010
Europe	122,979	7,969	130,948
Italy	14,032	2,120	14,152

Patients and Methods

Case Selection

We included in our analysis 2,952 consecutive cases for which pathological material (biopsies taken from bone marrow, lymph-node or other tissues) was referred to the Hematopathology Unit of the IRCCS S. Orsola- Malpighi Academic Hospital for diagnosis within a 36 months period of time. Cases referred for second opinion were excluded in order to avoid the selection bias favoring more difficult diagnoses (e.g., rarer subtypes). Similarly, relapses and staging samples (i.e. consecutive material for the same patient) were excluded. Non-lymphoma diagnoses were then excluded.

Furthermore, in order to ensure a balanced ratio among cases from northern, central and southern Italy, cases from the three areas were included, roughly covering similar population amounts based on the population sizes of those areas. Finally, the availability of the basic demographic information including at least age, gender, and site of origin was requested for enrollment.

All cases were centrally diagnosed, all tissue samples being studied by histological examination by at least two well-experienced hematopathologists. The diagnoses were established according to the WHO classification.

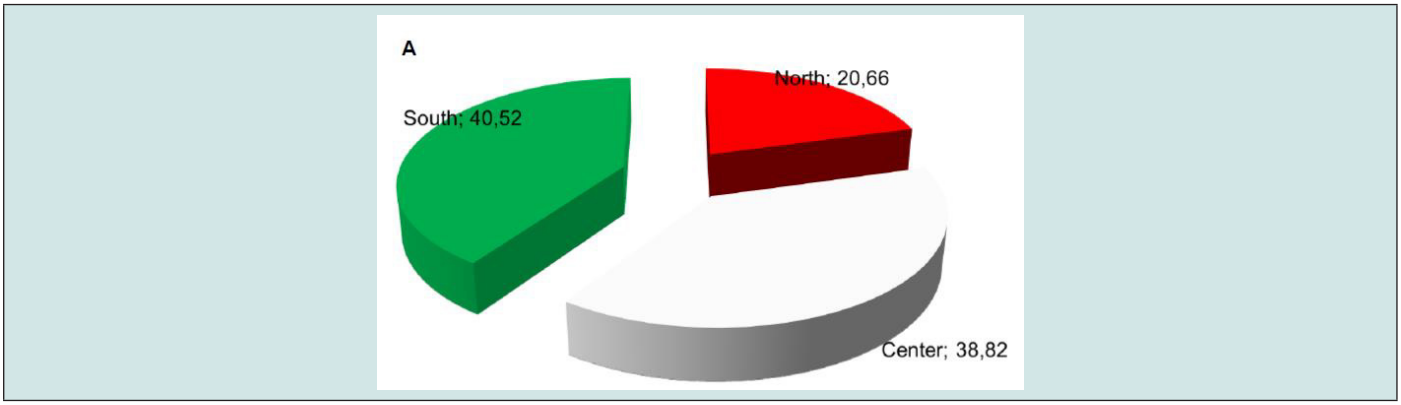
Statistical Analysis

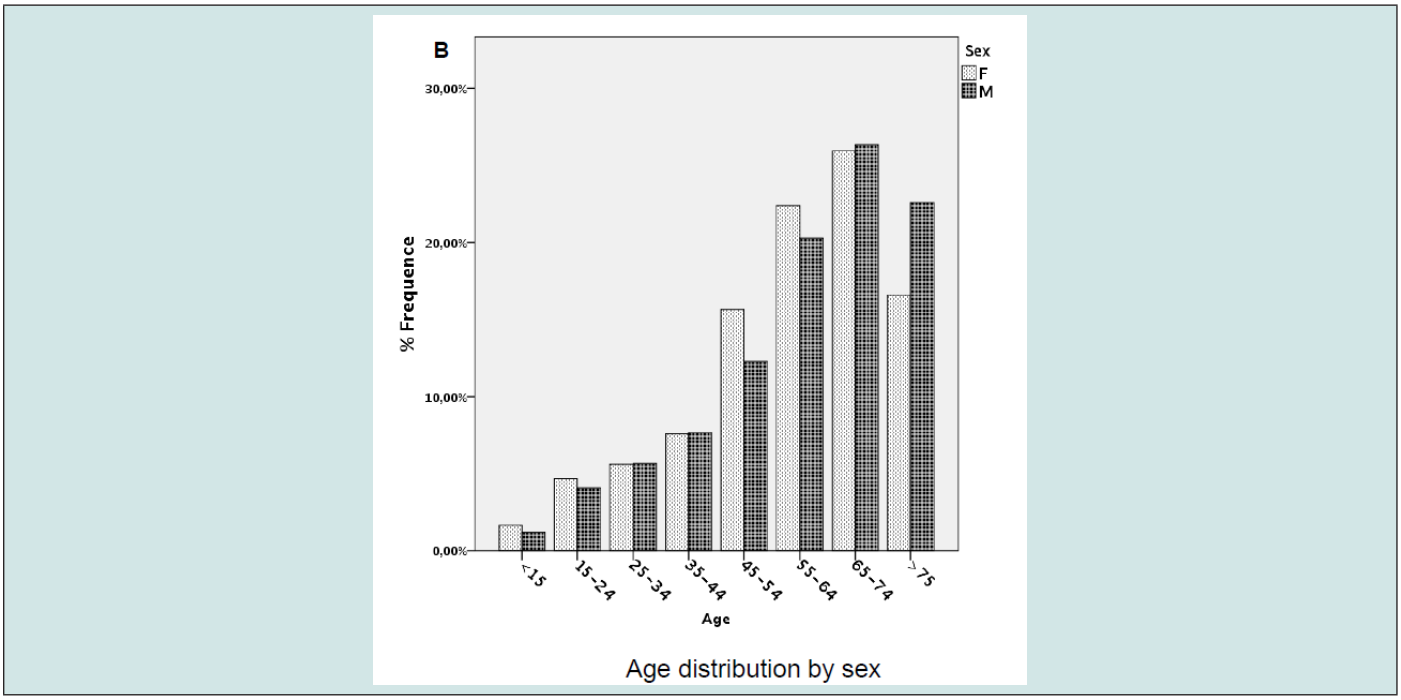
Statistical analyses were performed using IBM SPSS Statistics 20.0 and Prism (GraphPad software, USA). ANOVA and unpaired T-tests were used for continuous variables examination. When a sample size was less than 10 cases in at least 1 group a non-parametric (Mann-Whitney) test was used. Chi-square (or the non-parametric Fisher exact test when indicated) was used for dichotomic variables analyses [6,7].

Results

Lymphoma Incidence Rates Varies by Gender and Age

We analyzed 2,952 lymphoma cases diagnosed over a period of 36 months, corresponding to a mean of 983 cases per year and therefore to roughly 7% of all national cases. No significant differences were recorded in terms of number of cases during the study period. Despite the selection of Hospitals enrolling comparable populations in the three geographical areas, we observed a moderate imbalance among the different areas. Particularly, 40.52% of cases were from southern Italy, 38.82% from central, and only 20,66% from the north (Figure 3A). The mean age at diagnosis was 59.6 (range 5-90). Lymphomas were equally distributed in males and females (1,478 vs. 1,474 cases), with progressive increase of incidence by age (Figure 3B). The same trend was observed in the three geographical areas (Figure 3C).





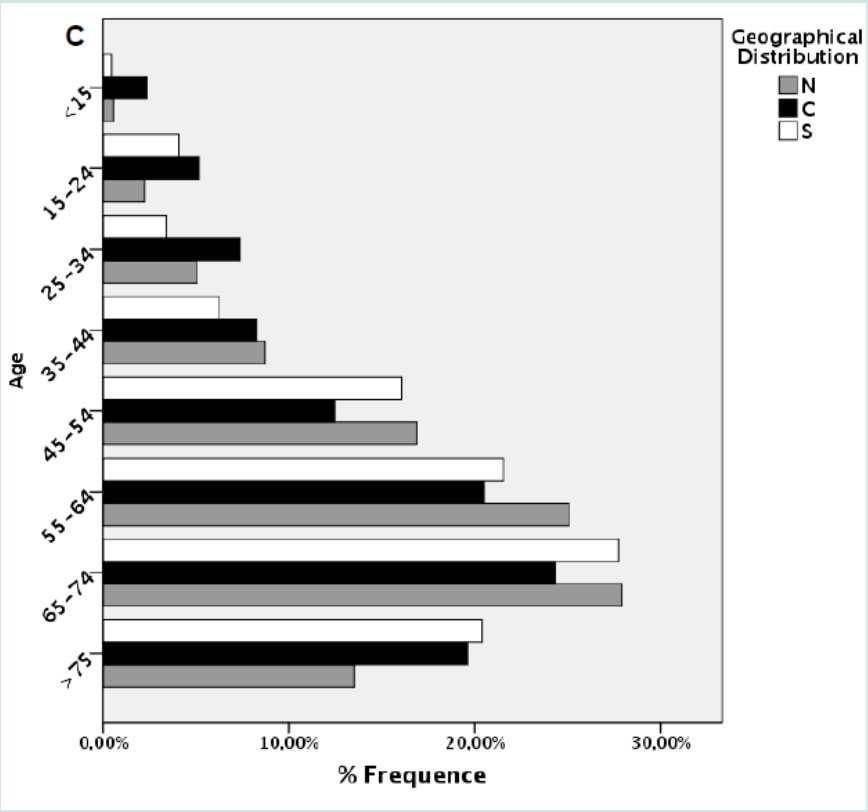
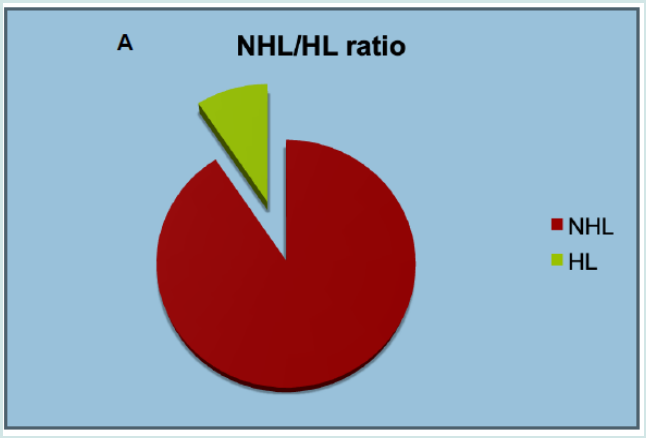
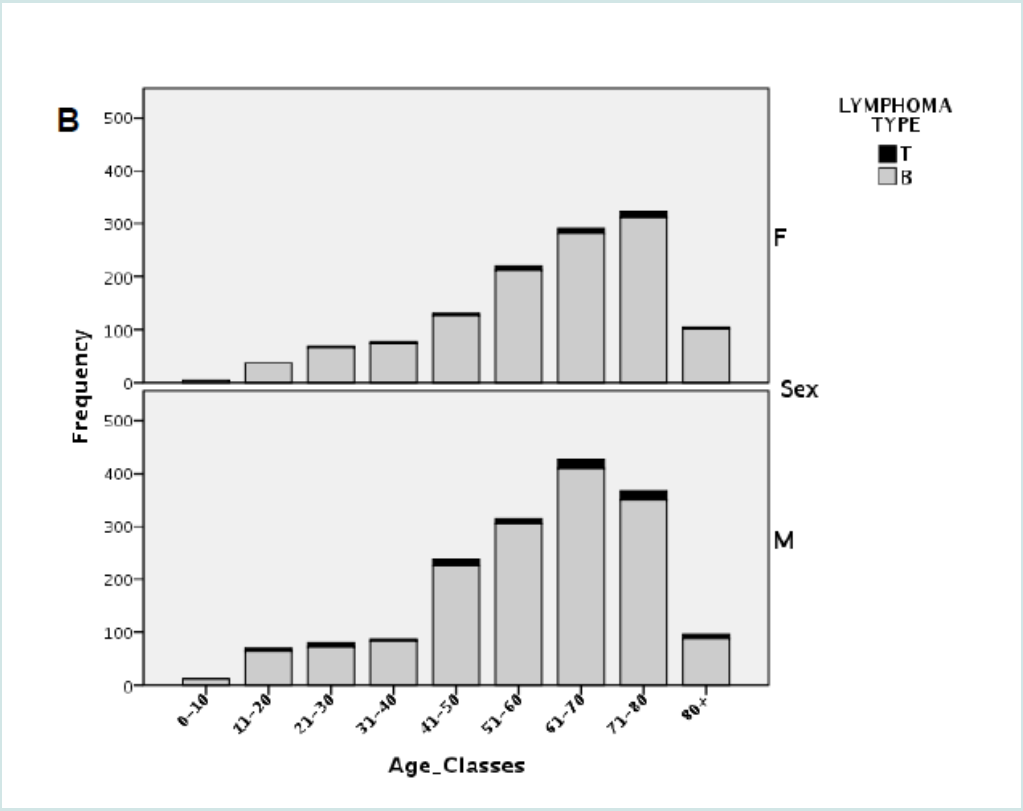


Figure 3: A) Distribution of cases by geographical areas. B) Frequency of lymphomas by age and gender. C) Frequency of lymphomas by age and gender by geographical areas.

Incidence of Lymphomas by Subtype

NHL represented 90,67% of cases, while 9.33% were HL (Figure 4A). As expected, B-cell malignancies were the commonest in all age groups, representing 96.09% of all cases (Figure 4B). Overall, the most frequent lymphoma was diffuse large B-cell lymphoma (DLBCL), representing 19.94% of cases, followed by follicular lymphoma (FL, 18.55%), chronic lymphocytic leukemia (CLL, 18.31%), and plasmacytoma (8.99%) (Figure 4C & Table 2). Males and females had overall a similar incidence of lymphoma (M/F ratio being about 1). However, some differences were observed across specific subtypes. Among B-cell neoplasm, male predominance was particularly increased for hairy cell leukemia (HCL), with a male/female (M/F) ratio of 5.35, mantle cell lymphoma (2.47) and lymphoblastic lymphoma (2.1). Classical Hodgkin lymphomas (cHL) were slightly more frequent in females (M/F=0.78), while the lymphocyte predominant type was not (M/F=1.47). Among T-cell neoplasm, the M/F ratio was increased in ALK- anaplastic large cell lymphoma (ALCL, 2.96) and peripheral T-cell lymphoma not otherwise specified (PTCL/NOS, 1.73), while angioimmunoblastic T-cell Lymphoma was more frequent in women (M/F=0.59).





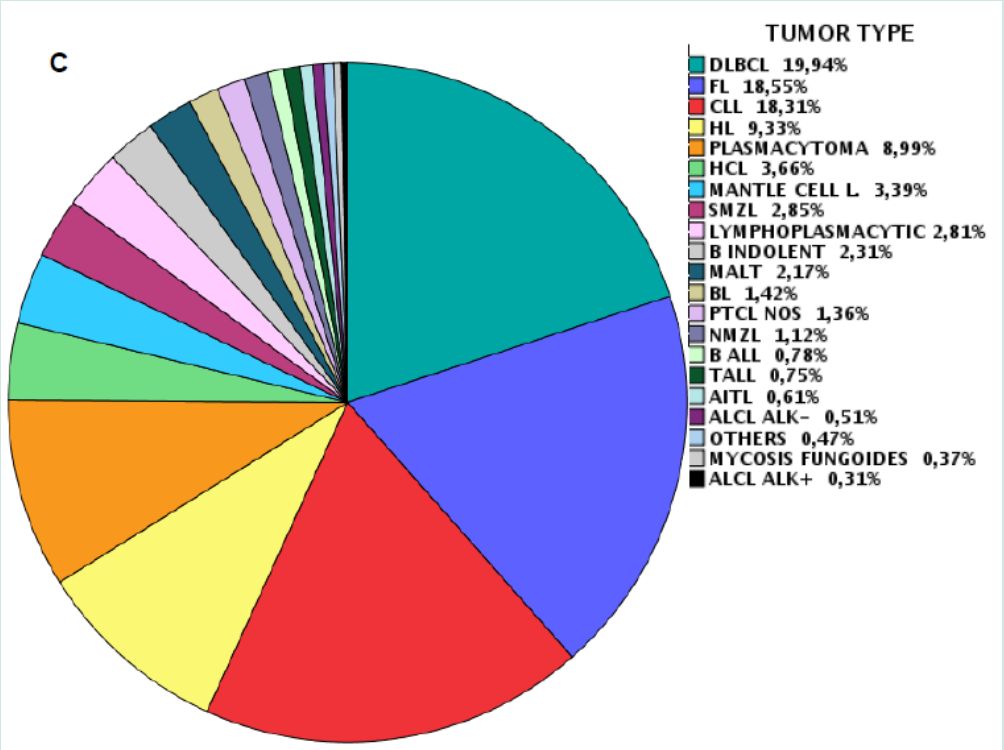


Figure 4: A) Incidence of B-cell and T-cell lymphomas by age group. B) Relative frequency of HL and NHL. C) Relative frequency of lymphoma subtypes.

Table 2: Relative frequency of lymphoma subtypes.

Tumor Types	%	cases
DLBCL	19.94	589
FL	18.55	548
CLL	18.31	541
HL	9.33	275
PLASMACYTOMA	8.99	265
HCL	3.66	108
MCL	3.39	100
SMZL	2.85	84
LPL	2.81	83
B INDOLENT NOS	2.31	68
MALT	2.17	64
BL	1.42	42
PTCL NOS	1.36	40
NMZL	1.12	33
B ALL	0.78	23
T ALL	0.75	22
AITL	0.61	18
ALCL ALK-	0.51	15
OTHERS	0.47	14
MYCOSIS FUNGOIDES	0.37	11
ALCL ALK+	0.31	9
Totale	**100**	**2952**

No Significant Differences Were Recorded Regarding Other Entities

As mentioned, the incidence of lymphoma was overall higher in elderly; however, as expected, this trend was not observed for some entities. Specifically, Burkitt lymphoma (BL), HL and both B-cell and T-cell lymphoblastic lymphomas were almost exclusively diagnosed in children, while other lymphoid neoplasms like MCL, marginal zone lymphoma (MZL) and CLL were quite rare in younger patients (Figure 5). As far as the geographical distribution was concerned, although for most subtypes no major differences were observed, some entities showed an apparently different distribution (chi square= 144.546; $p<0.001$ – calculated for entities reaching at least 20 cases in each group). Specifically, FL, DLBCL, and MALT lymphomas were more frequently encountered in Northern and Central Italy, while CLL and splenic MZL were commoner in the South (Table 3; Figures 6 & 7). Furthermore, plasmacytomas were commoner in Central Italy, while LPL was rarer in this part of the country. Finally, HCL was more often observed in the North, cHL was only slightly more frequent in the South, and BL was absolutely infrequent in this same area (Table 3, Figures 6 & 7).

Table 3: Lymphoma types of distribution in Northern, Central and Southern Italy.

Entity	South	Center	North	Total
DLBCL	151	232	206	589
FL	153	186	209	548
CLL	272	133	136	541
HL	101	90	84	275
PLASMACYTOMA	76	109	80	265
HCL	28	22	58	108
SMZL	43	17	24	84

MCL	33	31	36	100
LPL	31	16	36	83
MALT	10	30	24	64
INDOLENT B-NHL NOS	24	20	24	68
BL	3	25	14	42
PTCL/NOS	13	13	14	40
NMZL	8	8	17	33
B ALL	6	10	7	23
T ALL	10	5	7	22
AITL	6	8	4	18
ALCL ALK-	5	10	0	15
MYCOSIS FUNGOIDES	1	6	4	11
ALCL ALK +	3	1	5	9
OTHERS	4	4	6	14
TOTAL	**981**	**976**	**995**	**2952**

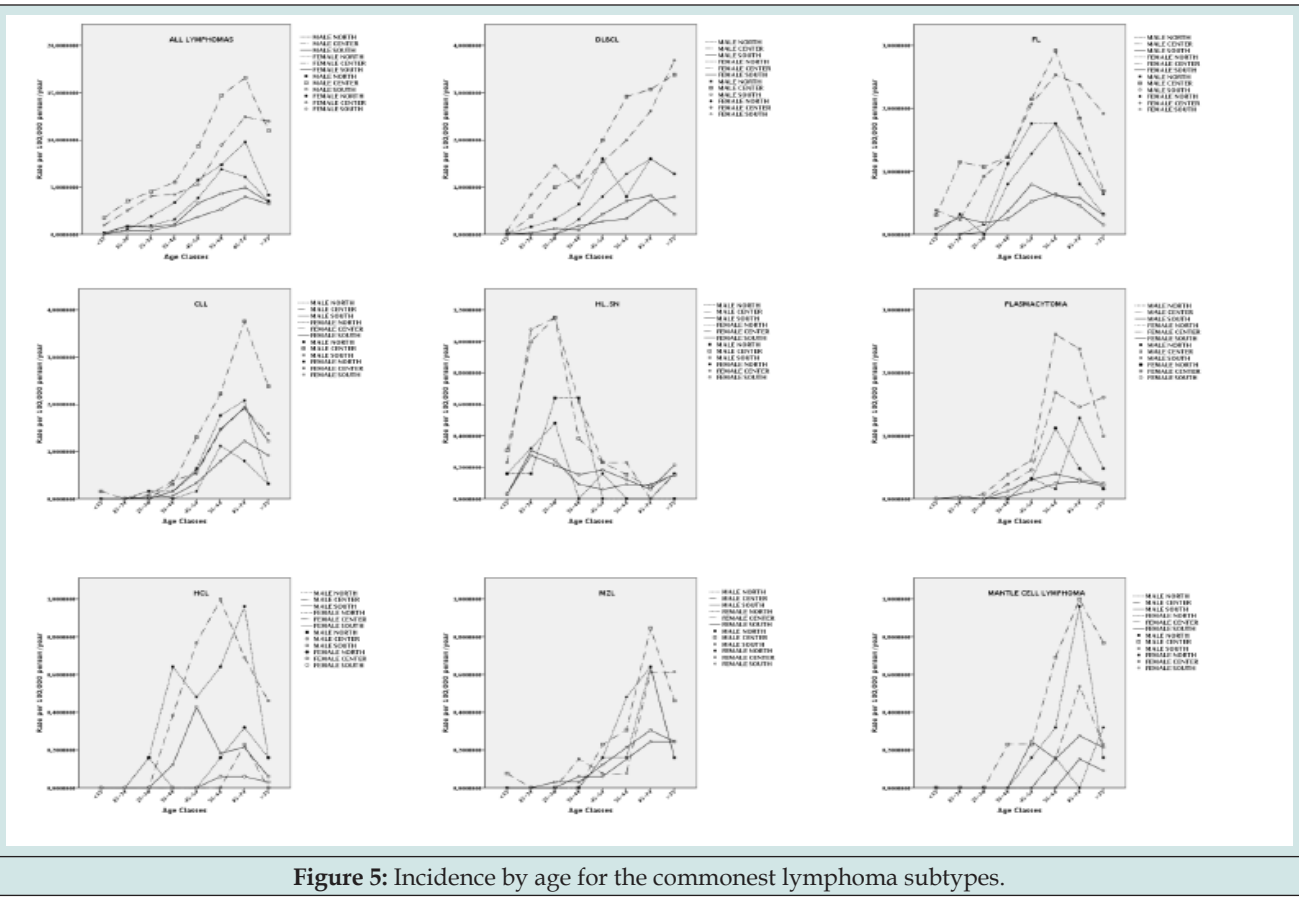


Figure 5: Incidence by age for the commonest lymphoma subtypes.

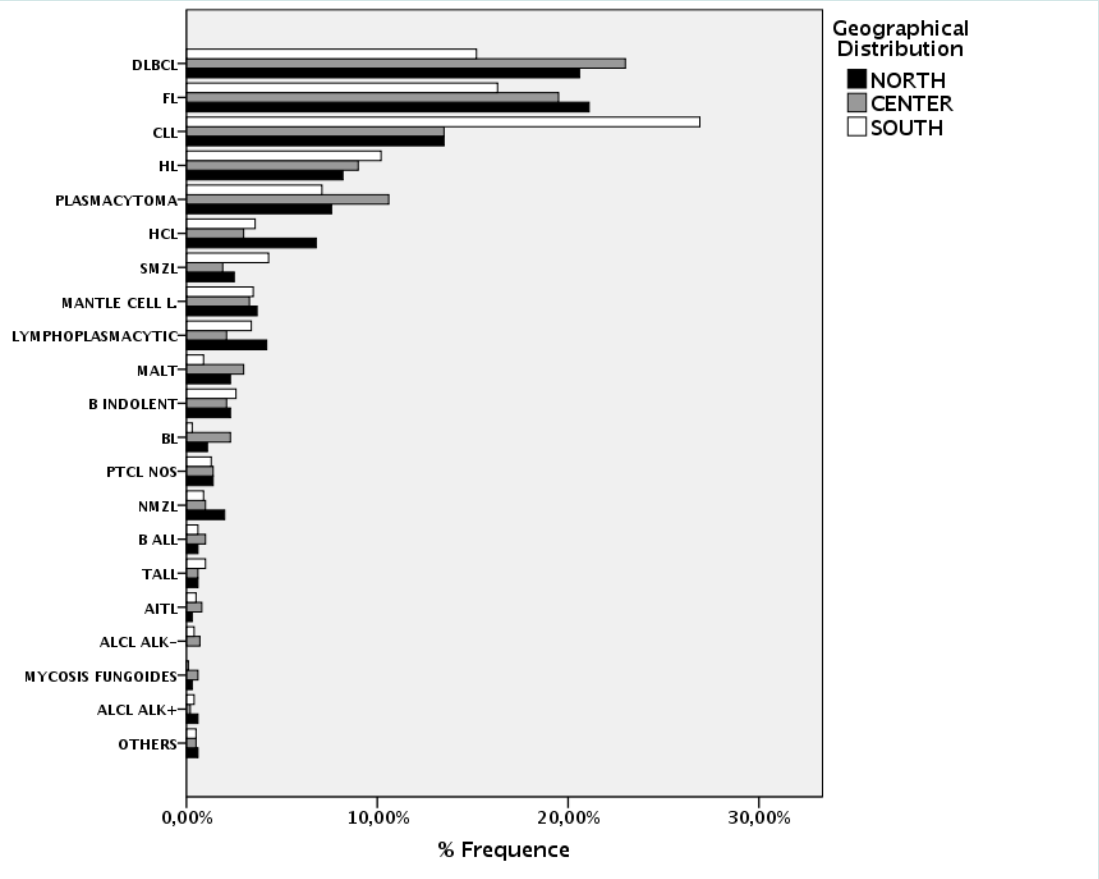
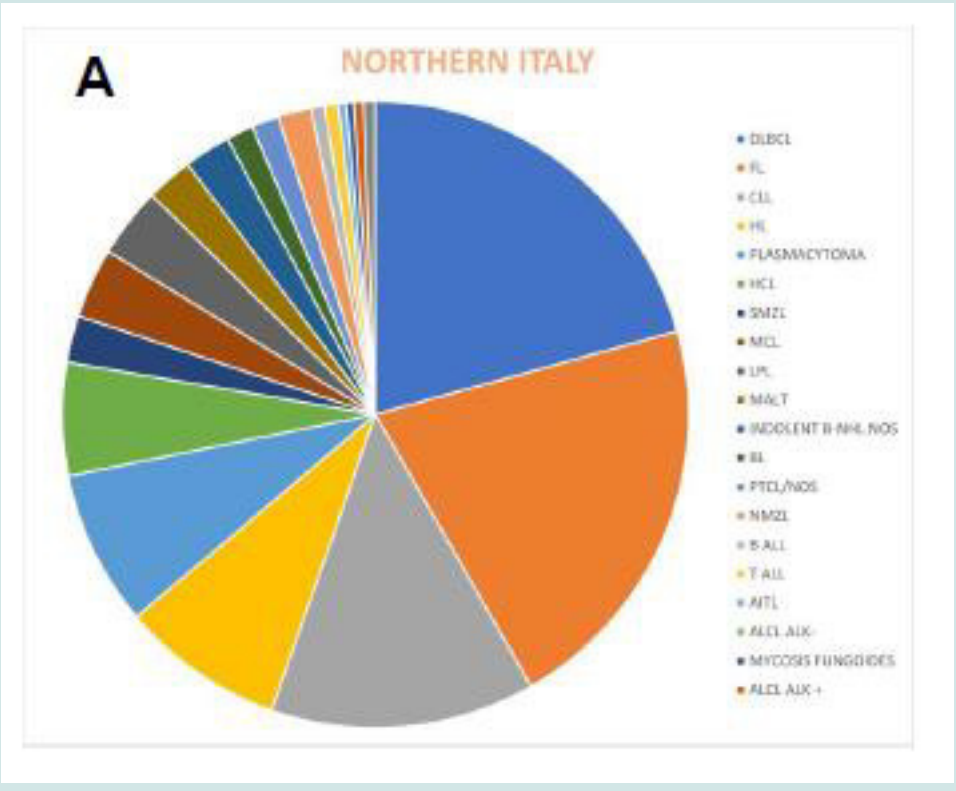
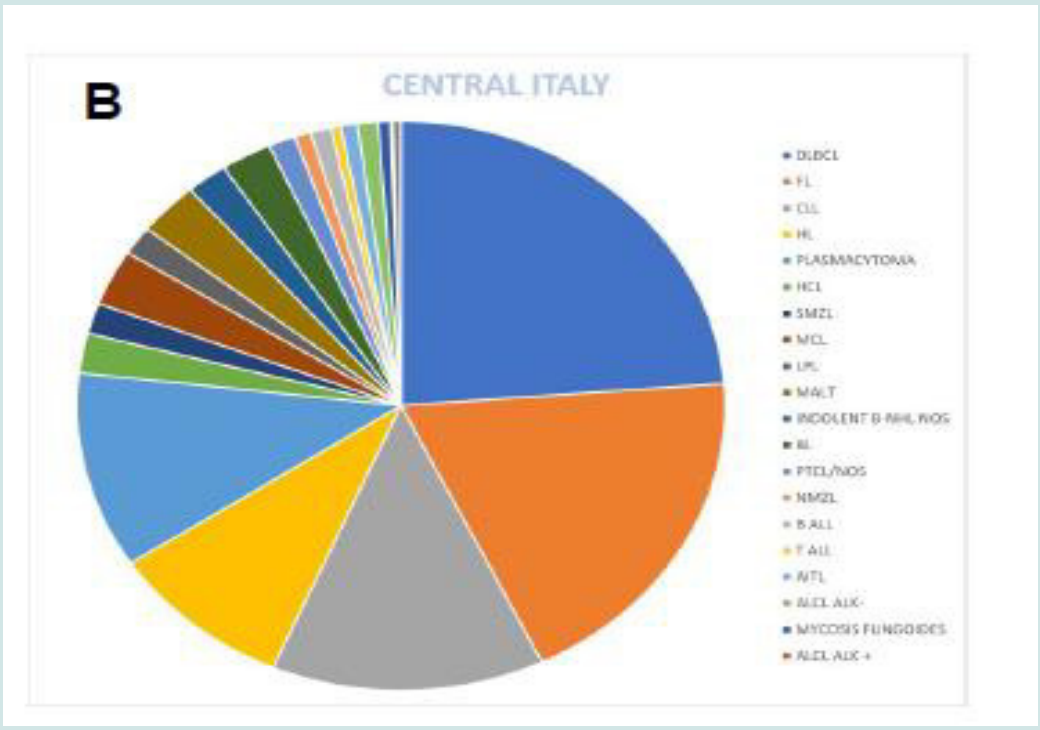


Figure 6: Relative frequency lymphoma subtypes by geographical area.





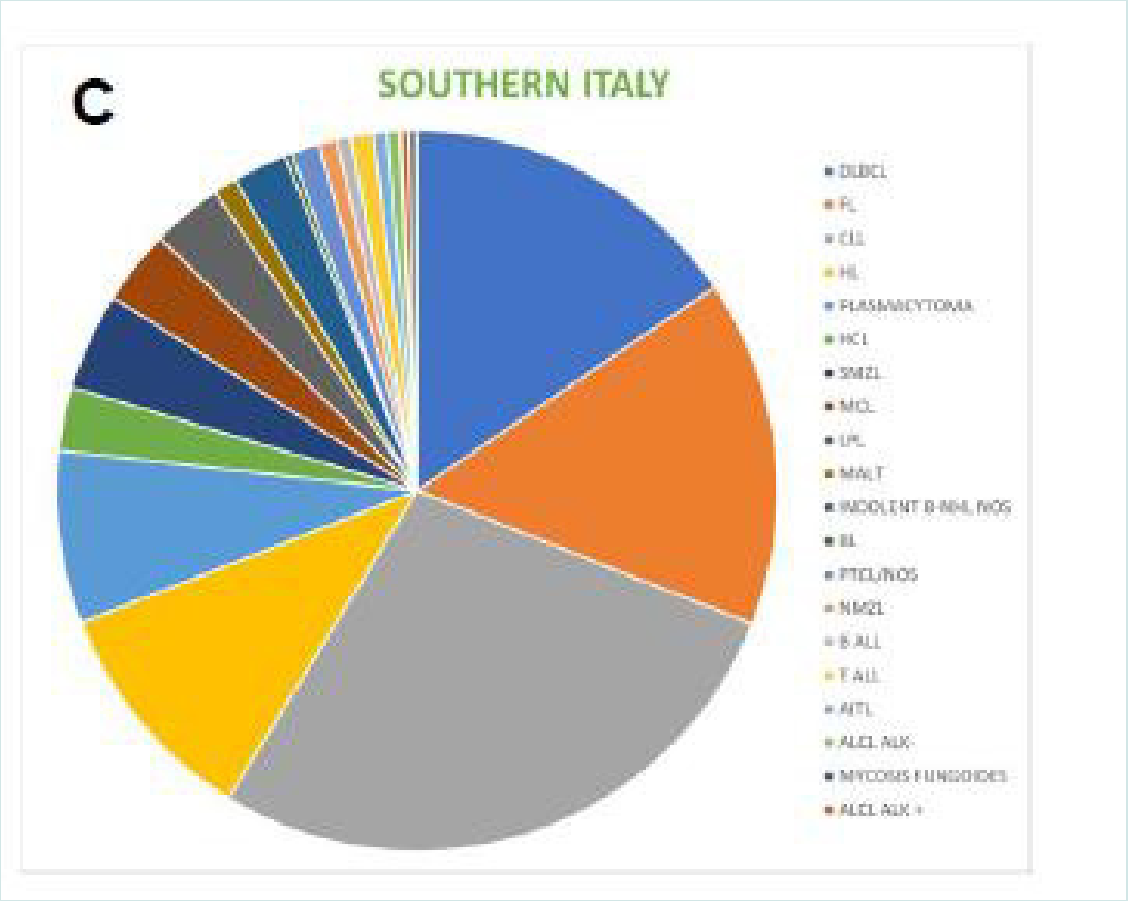


Figure 7: Relative frequency lymphoma subtypes in Northern (A), Central (B), and Southern (C) Italy.

Discussion

This is the first study addressing the epidemiology of malignant lymphomas in Italy, as classified by WHO classification, to the best of our knowledge. First, we showed that Italian patients are like other European as well as to Americans in terms of age at onset and gender. Specifically, a progressive increase in lymphoma incidence was noted according to age, most cases being diagnosed in adults and elderly. However, as expected, HL and LBL were indeed more common in younger patients. By contrast, in Africa several reports indicated a younger age at presentation for different lymphoproliferative disorders, including entities usually rare in young adults, such as CLL [8,9] Consistent with the WHO classification, we found a striking male predominance in HCL cases and, at lower extent, in MCLs [3-11]. Conversely, cHL was more frequent in women, as already described [12]. Of interest, AITL was also found to be slightly more common in female, differently from what reported so far in other Western Countries and Asia [13,14]. Furthermore, a significantly older age at diagnosis was recorded in female AITL patients (69 years vs. 60.87 years in males) [13,14]. In addition, we observed that ALCL ALK- was almost three time more frequent in men than in women, this being in contrast with most recent literature data on case collected in western counties [15]. Nonetheless, the mean age of presentation was in line with literature data, being significantly higher than what recorded for ALK+ cases (57.73 vs. 49.77 years) [14,15]. Concerning ALCL, no breast implant associated cases were diagnosed in the considered time frame.

Cases were collected at reference centers across the Country, including Northern, Central and Southern Italy, to ensure an adequate picture. Indeed, this is not trivial, since the climatic, environmental as well as nutritional difference might affect incidence of the diseases. In our analysis, we observed a difference in the relative frequency of some common entities. While DLBCL and FL were the commonest entities in Northern and Central Italy, CLL was largely the commonest in the Southern regions. This might of course reflect a real higher incidence of the disease or, alternatively, may be the consequence of a different approach to CLL diagnosis at different centers. In fact, CLL is more commonly diagnosed by hematologists based on peripheral blood immunophenotyping at most Italian centers. However, our data may indicate that CLL diagnosis is often achieved by bone marrow/lymph node histological examination in many Southern Italy hospitals. It should be noted, nonetheless, that the European cancer registry-based project on hematological malignancies (HAEMACARE), including data from all European countries, reported CLL as the most common lymphoid neoplasm, followed by DLBCL and FL [4]. Again, this data may reflect a more comprehensive analysis of diagnostic tools, including flow cytometric analysis of peripheral blood to identify patients affected by CLL.

According to the latest WHO classification, the most common NHL in Western countries is DLBCL, representing about 31% of cases in adults, followed by FL (22%), MZL (8%), MCL and CLL/SLL (6% each), BL (2%), and lymphoplasmacytic lymphoma (LPL) (1%) (16–18)T-cell derived lymphomas account for only 10–15% of all NHL, PTCL/NOS, angioimmunoblastic T-cell lymphoma (AITL) and cutaneous forms being the commonest [19,20]. However, several works aiming to define the epidemiology of lymphomas in selected geographical areas have been produced in the past decade, challenged this scenario, indicating peculiar patterns. In general, a lower incidence of lymphoid malignancies was observed in Asian populations, particularly concerning FL CLL, and HL. On the other hand, a higher incidence of marginal zone lymphoma (MZL) and extra-nodal NK/T-cell lymphoma (ENKTL), nasal type was documented [21-23]. The Korea Central Cancer Registry (KCCR) reported that lymphoid malignancies represented about 3% of all cancers, with increased incidence between 1999 and 2012, DLBCL, MZL and peripheral T-cell lymphomas not otherwise specified being the commonest entities [24]. A large Japanese study showed that the incidence of FL and methotrexate-associated lymphoproliferative disorders increased during the analyzed time frame (2007-2014) [25] Interestingly, the authors observed that the onset age appeared increased for both FL and DLBCL over time [25]. Further, a significantly higher incidence of T-cell lymphomas was recorded, ranging between 12% and 33% in the different considered provinces [25]. As far as Latin America was concerned, a national study from Colombia showed that most NHL were aggressive, mostly DLBCL [26]. Of note, HL appeared to be more common than FL, while T-cell neoplasms were definitely rare [26]. The International Non-Hodgkin Lymphoma Classification Project extensively investigated the epidemiology of lymphomas in Southern-Africa [27] that similarly to what described in Colombia, Southern Africa had a significantly higher prevalence of aggressive vs. of indolent NHL (51.5 vs. 34.3%) if compared to Europe and Northern-America. Particularly, high grade B-cell lymphomas (formerly Burkitt-like lymphomas) were significantly more common in Southern Africa (8.2%) than in Europe (2.4%) and Northern-America (2.5%), being frequently associated with HIV infection [27]. Of interest, whites presented with significantly higher frequency of indolent B-NHL (60.4%) and a lower frequency of aggressive B-NHL (32.7%) compared to blacks (22.5% vs. 62.6%) [27]. Specifically, whites had a significantly higher frequency of FL and a lower frequency of high-grade B-cell lymphomas compared to blacks [27]. Furthermore, the median age at onset was significantly higher in whites than in blacks, as far as indolent, aggressive B-NHL as well as T-NHL (64, 56 and 67 years vs. 55, 41 and 34 years, respectively). Similar patterns were observed in Eastern Africa, as reported by Dr. Rogena and Colleagues [28], and Egypt, where again indolent disorders like FL and CLL represented together only 15% of the total [24]. The major limitations of our analysis are certainly represented by the lack of many clinical as well as social information that would be useful to interpret the results. Indeed, different frequency of certain diseases in different geographical area might be due to different exposure to risk factors. Second, although collecting cases from a remarkable

part of the country, covering North, Center, and South, this is not properly a national registry-based study. Certainly, a study covering these two issues is warranted. However, on the other hand, we provided a series of unprecedented information regarding lymphomas in Italy. In conclusion, our study described for the first time the basic information about lymphoma epidemiology in Italy after WHO 2017 was released. It underlined the importance of national registries and local epidemiological analyses; in fact, a better knowledge of regional peculiar situations can be the basis for local specific intervention and global health care improvement [29].

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