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ORIGINAL PAPER

Incidence and time trends of childhood lymphomas: findings from 14 Southern and Eastern European cancer registries and the Surveillance, Epidemiology and End Results, USA

Marios K. Georgakis[1] · Maria A. Karalexi[1] · Domenic Agius[2] · Luis Antunes[3] · Joana Bastos[4] · Daniela Coza[5] · Anna Demetriou[6] · Nadya Dimitrova[7] · Sultan Eser[8] · Margareta Florea[9] · Anton Ryzhov[10] · Mario Sekerija[11] · Tina Žagar[12] · Anna Zborovskaya[13] · Snezana Zivkovic[14] · Evdoxia Bouka[1] · Prodromos Kanavidis[1] · Helen Dana[15] · Emmanuel Hatzipantelis[16] · Maria Kourti[17] · Maria Moschovi[18] · Sophia Polychronopoulou[19] · Eftichia Stiakaki[20] · Maria Kantzanou[1] · Apostolos Pourtsidis[21] · Eleni Th. Petridou[1]

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Abstract

Purpose To describe epidemiologic patterns of childhood (0–14 years) lymphomas in the Southern and Eastern European (SEE) region in comparison with the Surveillance, Epidemiology and End Results (SEER), USA, and explore tentative discrepancies.

Methods Childhood lymphomas were retrieved from 14 SEE registries ($n = 4{,}702$) and SEER ($n = 4{,}416$), diagnosed during 1990–2014; incidence rates were estimated and time trends were evaluated.

Results Overall age-adjusted incidence rate was higher in SEE ($16.9/10^6$) compared to SEER ($13.6/10^6$), because of a higher incidence of Hodgkin (HL, $7.5/10^6$ vs. $5.1/10^6$) and Burkitt lymphoma (BL, 3.1 vs. $2.3/10^6$), whereas the incidence of non-Hodgkin lymphoma (NHL) was overall identical ($5.9/10^6$ vs. $5.8/10^6$), albeit variable among SEE.

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✉ Eleni Th. Petridou
epetrid@med.uoa.gr

[1] Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias Str, 11527 Athens, Greece

[2] Department of Health Information and Research, Malta National Cancer Registry, Pieta, Malta

[3] North Region Cancer Registry of Portugal (RORENO), Portuguese Oncology Institute of Porto, Porto, Portugal

[4] Central Region Cancer Registry of Portugal (ROR-Centro), Portuguese Oncology Institute of Coimbra, Coimbra, Portugal

[5] Regional Cancer Registry of Cluj, Oncological Institute "Ion Chiricuta", Cluj-Napoca, Romania

[6] Cyprus Cancer Registry-Health Monitoring Unit, Ministry of Health, Nicosia, Cyprus

[7] Bulgarian National Cancer Registry, National Oncology Hospital, Sofia, Bulgaria

[8] Izmir Cancer Registry, Izmir Hub, Izmir and Hacettepe University Institute of Public Health, Ankara, Turkey

[9] Regional Cancer Registry of Iaşi, National Institute of Public Health, Iaşi, Romania

[10] National Cancer Registry of Ukraine, National Institute of Cancer, Kiev, Ukraine

[11] Croatian National Cancer Registry, Croatian Institute of Public Health, Zagreb, Croatia

[12] Cancer Registry of Republic of Slovenia, Institute of Oncology, Ljubljana, Slovenia

[13] Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Childhood Cancer Subregistry of Belarus, Minsk, Belarus

[14] Institute of Public Health of Serbia, Belgrade, Serbia

[15] Oncology Department, Mitera Childrens Hospital, Athens, Greece

[16] Second Department of Pediatrics, AHEPA General Hospital, Aristotelion University of Thessaloniki, Thessaloníki, Greece

[17] Department of Pediatric Hematology and Oncology, Hippokration Hospital, Thessaloníki, Greece

[18] Haematology-Oncology Unit, First Department of Pediatrics, "Aghia Sophia" Children's Hospital, Athens University Medical School, Athens, Greece

Incidence increased with age, except for BL which peaked at 4 years; HL in SEE also showed an early male-specific peak at 4 years. The male preponderance was more pronounced for BL and attenuated with increasing age for HL. Increasing trends were noted in SEER for total lymphomas and NHL, and was marginal for HL, as contrasted to the decreasing HL and NHL trends generally observed in SEE registries, with the exception of increasing HL incidence in Portugal; of note, BL incidence trend followed a male-specific increasing trend in SEE.

Conclusions Registry-based data reveal variable patterns and time trends of childhood lymphomas in SEE and SEER during the last decades, possibly reflecting diverse levels of socioeconomic development of the populations in the respective areas; optimization of registration process may allow further exploration of molecular characteristics of disease subtypes.

Keywords Lymphoma · Hodgkin's disease · Childhood · Incidence · Time trends · Cancer registration

Introduction

Lymphomas comprise a heterogeneous group of malignancies accounting for 10 % of total childhood (0–14 years) cancer, traditionally classified as Hodgkin's (HL) and non-Hodgkin lymphoma (NHL) [1]. HL, representing approximately 40 % of childhood lymphomas, peaks in adolescence and is rarely diagnosed before the age of 10 years [2], whereas NHL is primarily diagnosed in late adulthood and accounts for 6 % of childhood malignancies. The most common NHL subtypes in childhood are Burkitt (BL) and large B cell lymphomas [1]; the distinct morphological, epidemiologic, and etiologic properties of BL in childhood, however, have led to a further distinction and separate classification from other NHL in the International Classification of Childhood Cancer, 3rd Edition (ICCC-3) [3–5]. The etiology of lymphoma etiology remains largely unknown; several risk factors have been identified in recent years, however, with infectious agents, mainly Epstein Barr Virus (EBV), implicated into the pathogenic processes [6–8].

Epidemiologic studies on childhood lymphoma incidence and time trends show geographical disparities [9–18], which have been conventionally attributed to the socioeconomic development level of the studied populations [19–22]. In particular, higher HL incidence rates have been reported in developing countries [9]; overall incidence in Europe is estimated around 5.8 cases per million [12], whereas rates are highly variable in other developed countries [23, 24] and between geographical subregions [12]. An approximate incidence of 10 cases per million of childhood NHL (including BL) has been estimated in developed countries with increasing trend in both USA and Europe [1, 25]. Similarly to HL, the rates of NHL are higher in developing countries, especially in malaria-endemic regions, mainly on account of the higher incidence of endemic BL [13, 16, 17]. Specific age and gender patterns have been described for lymphoma subtypes; interestingly though, these patterns also vary by geographical region and studied population [1, 12, 25, 26].

The main aim of the current study was to present, for the first time, cross-country comparisons of the incidence and time trends, as well as the distribution of demographic and disease-specific characteristics of childhood lymphomas in Southern and Eastern Europe (SEE). Primary data for this area that is rather underrepresented in the published literature were contributed by an informal network of population-based cancer registries geared to enhance scientific research in the context of the EUROCOURSE project [27]. In order to evaluate the previously reported geographical and socioeconomic discrepancies, we also opted to conduct comparisons with the more economically developed US population via the publicly available SEER data [28, 29].

Methods

Participating registries

A total of 14 cancer registries (Belarus, Bulgaria, Croatia, Cyprus, Greece, Malta, Central Portugal, North Portugal, Romania-Cluj, Northeast Romania, Serbia, Slovenia, Ukraine, Turkey-Izmir) operating in 12 countries comprised the informal SEE network coordinated by the Nationwide Registry of Childhood Hematological Malignancies and Brain Tumors (NARECHEM-BT) in Greece. Following common approval of a predefined protocol, the participating registries provided primary demographic data on childhood (0–14 years) lymphoma cases, diagnosed during study periods (detailed in Table 1) extending from 1990 to 2014; the data included information on gender, age, diagnosis, and morphology along with the respective childhood populations stratified by age and gender.

In addition, data on childhood lymphoma cases were extracted from the SEER database [28, 29], following exchange of a Research Data Agreement. The SEER data cover 18 registries (Atlanta, Connecticut, Detroit, Hawaii,

[19] Department of Pediatric Haematology-Oncology, "Aghia Sophia" Children's Hospital, Athens, Greece

[20] Department of Pediatric Hematology-Oncology, University Hospital of Heraklion, University of Crete, Heraklion, Greece

[21] Department of Pediatric Hematology-Oncology, "Pan. & Agl. Kyriakou" Children's Hospital, Athens, Greece

Table 1 Characteristics and quality of registration indicators of childhood (0–14 years) lymphoma cases derived from the 14 participating Southern and Eastern Europe cancer registries and the Surveillance, Epidemiology, and End Results Program (SEER), USA

Country and registry *Name*	Time period	Registration method	Coverage	National childhood population covered (%)	Urban (%)	Ethnic diversity	DCOs (%)	MVs (%)	Unspecified histology (%)
Belarus *Childhood Cancer SubRegistry of Belarus*	1990–2014	Passive (1986–1998) and active, (1999) IARC standardized registration	National	~100	73	Belarusian 84 %, Russian 8 %, Polish 3 %, Ukrainian 2 %, Other 3 %	0.2	97.6	0.1
Bulgaria *Bulgarian National Cancer Registry*	1990–2013	Predominantly active, IARC standardized registration	National	95	73	Bulgarian 84 %, Turk 9 %, Roma 5 %, Other 2 %	4.3	75.5	4.7
Croatia *Croatian National Cancer Registry*	2001–2013	Predominantly passive, IARC standardized registration, complemented by active registration data provided by physicians through electronic hospital files and pathology reports	National	~100	56	Croatian 90 %, Serbian 4 %, Bosnian 1 %, Other 5 %	0.0	96.5	1.1
Cyprus *Cyprus Cancer Registry*	1998–2011	Active, IARC standardized registration	National	~100	67	Greek Cypriot 72 %, Turkish-Cypriot 9 %, Foreign resident 18 %, Armenian, Maronite, and Latin 1 %	1.8	95.5	3.5
Greece *Nationwide Registry of Childhood Hematological Malignancies and Brain Tumors*	1996–2014	Active hospital based, IARC/ENCR standardized registration	National	~100	73	Greek 92 %, Albanian, 4 %, Other, 4 %	0.0	100.0	0.0
Malta *Malta National Cancer Registry*	1996-2013	Active and passive hospital based registration	National	~100	95	Maltese 95 %, British 2 %, Other 3 %	0.0	96.8	0.0
Portugal (Central) *The Centre Region of Portugal Cancer Registry*	1990–2010	Active, IARC standardized registration, data entered in the Web-based ROR	Regional	23	50	Portuguese 97 %, Other 3 %	0.0	92.4	2.8

Table 1 continued

Country and registry *Name*	Time period	Registration method	Coverage	National childhood population covered (%)	Urban (%)	Ethnic diversity	DCOs (%)	MVs (%)	Unspecified histology (%)
Portugal (North) *The North Region of Portugal Cancer Registry*	1995–2010	Active, IARC standardized registration, data entered in the Web-based ROR	Regional	32	73	Portuguese 98 %, Other 2 %	0.0	99.2	2.7
Romania (Cluj) *Cluj Regional Cancer* Registry	2006–2011	Passive registration, electronic/paper format data checked (IACRcrg), coded, and XL entered	Regional	13	55	Romanian 89 %, Hungarian 7 %, Roma 3 %, Other 1 %	0.0	89.3	0.0
Romania (Northeast) *Nord East Regional Cancer Registry of Romania*	2008–2010	Passive registration, electronic/paper format data checked (IACR.crg), coded and XL entered	Regional	17			4.2	87.5	0.0
Serbia *Central Serbia Cancer Registry*	2000–2011	Active and passive electronic (1998-) IARC/ENCR standardized registration	Regional	77	~50	Serb 83 %, Hungarian 4 %, Roma 2 %, Other 11 %	1.2	68.7	1.8
Slovenia *Cancer Registry of Slovenia*	1990–2011	Passive, IARC standardized a registration, online linkage to Central Population Register	National	100	50	Slovene 83 %, Serb 2 %, Croatian 2 %, Bosnian 1 %, Other, 12 %	0.0	85.0	0.7
Turkey (Izmir) *Izmir Cancer Registry*	1996–2012	Active registration, using approved quality control protocols	Regional	5	94	Turk: ~100 %,	0.4	87.9	1.1
Ukraine *National Cancer Registry of Ukraine*	2000–2012	Active registration, using approved quality control protocols	National	100	69	Ukrainian 78 %, Russian 17 %, Other 5 %	0.0	82.7	3.9
USA *Surveillance, Epidemiology, and End Results Program*	1990–2012	Active registration, using approved quality control protocols	Regional	29	77	White 64 %, Afro-American 12 %, Asian 9 %, American Indian/Alaska Native 1.5 %, Other 13.5 %	0.1	98.9	1.9

DCOs death certificate only diagnoses, *MVs* morphologically verified diagnoses, *IARC* International Agency for Research on Cancer

Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, Greater Georgia) for the period 1973–2012; for comparative reasons with the SEE data, only those diagnosed from 1990 onwards were included in the analyses.

Morphological classification

The morphological classification of lymphoma cases was based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) [30]. For the present analysis, cases were classified by ICD-O-3 coding to the following diagnostic subtypes of the ICCC-3 group II

classification: IIa (HL), IIb (NHL-excluding BL), IIc (BL), and IIe (unspecified lymphomas) [3]. Cases in the IId subgroup (miscellaneous lymphoreticular neoplasms) were excluded from the analysis, as non-lymphoma diagnoses. Thereafter, HL cases were subclassified to nodular sclerosis (ICD-O-3 coding: 9661, 9663–67), mixed cellularity (ICD-O-3 coding: 9652), lymphocyte rich (ICD-O-3 coding: 9651), nodular lymphocyte predominant (ICD-O-3 coding: 9659), lymphocyte depleted (ICD-O-3 coding: 9653–55), and HL not otherwise specified (NOS; ICD-O-3 coding: 9650). Due to the high proportion of NHL NOS cases in the SEE registries, no further classification of NHL was used.

Statistical analysis

Crude incidence rates were calculated along with overall age-standardized incidence rates per million children using the world (Segi) standard population for the age groups 0–4, 5–9, and 10–14 years by gender and specified diagnostic groups (IIa, IIb, IIc) [31]. Incidence rates were calculated separately for each SEE registry and for all participating SEE registries combined, as well as for SEER. The population estimates by age groups were obtained from each SEE registry, as provided by the respective national statistical services, whereas they are publicly available for SEER. Annual percent changes (APC) of incidence rates along with 95 % confidence intervals (CI) were estimated using Poisson regression analysis considering the number of cases in each year and the population as an offset variable. In order to identify potential breaks in trends, Joinpoint regression analyses were performed. Besides the individual effect estimated for each SEE registry, temporal trends were also evaluated for all participating SEE registries combined during the periods 1990–2012, as to increase statistical power and allow the emergence of significant trends [32]. SAS statistical software (version 9.2, SAS Institute Inc, Cary, NC, USA) and Joinpoint Regression Program (version 4.1.1—August 2014; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) were used for all statistical analyses.

Results

Quality indicators of registries and distribution of cases by study variables

A total of 4,702 childhood lymphoma cases were delivered by the 14 participating SEE registries (1990–2014), and 4,416 cases were extracted from the 18 SEER registries (1990–2012) yielding a grand total of 9,118 lymphomas. Table 1 presents the individual characteristics of the participating registries, along with quality indicators proposed by IARC [33]. Notably, 8 out of the 14 SEE registries had nationwide coverage, whereas SEER covered 29 % of the total childhood US population. Death certificate only (DCO) diagnoses represented <2 % in almost all registries and the percentage of morphologically verified (MV) diagnoses ranged from <70 % in Serbia to >95 % in 5 SEE registries and SEER. The proportion of unspecified cases (IIe subgroup) was low (range 0.0–4.7 %).

The distribution of lymphoma cases by age, gender, diagnostic subtype, and registry is presented in Table 2. Overall, males represented approximately two-thirds of all lymphoma cases, whereas their majority was diagnosed in the older age group (10–14 years). Among SEE registries, HL (IIa) comprised the most common (46.6 %) ICCC-3 diagnostic subtype, followed by NHL (IIb; 34.2 %). By contrast, NHL was the most common subtype in SEER.

Regarding the distribution of lymphoma histological subtypes, a different pattern was recorded for HL between SEE registries and SEER (Fig. 1), despite the overall higher proportion of NOS HL cases diagnosed in the former (27.87 vs. 10.3 %). Particularly, nodular sclerosis corresponded in SEE only to 36.9 % of HL cases, as opposed to 65.2 % in SEER, whereas the mixed cellularity subtype was more common in SEE representing 26 % of HL cases, compared to SEER (13 %). There were also amphidirectional differences in the lymphocyte-rich, nodular lymphocyte-predominant, and lymphocyte-depleted subtypes. The NHL histological subtypes were not examined given the extremely high proportion of NOS cases in SEE (40.7 vs. 7.2 % in SEER).

Incidence rates

The overall age-adjusted incidence rate for childhood lymphomas in SEE was $16.9/10^6$ children, significantly higher to that in SEER ($13.6/10^6$, $p < 0.001$). Among the diagnostic subgroups the incidence for HL in SEE ($7.5/10^6$) was significantly higher than SEER ($5.1/10^6$, $p < 0.001$), whereas no differences were documented for NHL between the two regions (5.9 vs. $5.8/10^6$); considerable variations within SEE registries was, however, noted. Similarly to HL, the incidence of BL in SEE was significantly higher compared to SEER ($3.1/10^6$ vs. $2.3/10^6$, respectively, $p < 0.001$) peaking in Izmir ($4.9/10^6$), the 2 Portuguese registries (4.5 and $4.4/10^6$), Belarus ($4.5/10^6$), and Greece ($4.4/10^6$) (Table 3).

Worth noting are the gender and age at diagnosis discrepancies by diagnostic subtype; the overall male/female age-adjusted incidence rate ratios were 1.6 for HL, 1.9 for NHL, and 3.8 for BL (Table 3), without considerable differences between SEE registries and SEER. Gender

Table 2 Distribution of demographic characteristics and histological subtype of childhood (0–14 years) lymphomas in the participating 14 cancer registries in Southern and Eastern Europe and the Surveillance, Epidemiology, and End Results (SEER), USA

Variable	Total $n = 9,118$ %	Belarus $n = 833$ %	Bulgaria $n = 530$ %	Croatia $n = 177$ %	Cyprus $n = 57$ %	Greece $n = 532$ %	Izmir $n = 273$ %	Malta $n = 23$ %	Central Portugal $n = 144$ %	North Portugal $n = 189$ %	Romania-Cluj $n = 28$ %	Northeast Romania $n = 24$ %	Serbia $n = 166$ %	Slovenia $n = 147$ %	Ukraine $n = 1,579$ %	SEE $n = 4,702$ %	SEER $n = 4,416$ %
Gender																	
Male	66.4	67.3	69.8	66.7	68.4	70.5	66.7	82.6	66.0	64.5	67.9	62.5	64.5	70.7	66.4	67.5	65.1
Female	33.6	32.7	30.2	33.3	31.6	29.5	33.3	17.4	34.0	35.5	32.1	37.5	35.5	29.3	33.6	32.5	34.9
Age (years)																	
<5	16.8	19.3	20.4	16.4	5.3	15.6	20.9	17.4	19.5	23.8	25.0	16.7	20.5	17.0	19.8	19.2	14.3
5–9	31.0	31.8	36.4	27.7	36.8	34.0	36.6	26.1	31.9	31.2	42.9	45.8	36.7	32.0	27.6	31.6	30.3
10–14	52.2	48.9	43.2	55.9	57.9	50.4	42.5	56.5	48.6	45.0	32.1	37.5	42.8	51.0	52.6	49.2	55.4
Diagnostic subtype (ICCC-3)																	
HL (IIa subgroup)	43.0	52.8	49.8	41.3	50.9	41.0	38.1	39.1	51.4	42.3	39.3	41.7	34.9	41.5	48.2	46.6	39.2
NHL-except BL (IIb subgroup)	38.1	23.3	36.2	43.5	38.6	32.9	38.1	39.1	22.9	34.9	35.7	45.8	55.4	40.1	35.7	34.2	42.3
BL (IIc subgroup)	16.8	23.8	9.3	14.1	7.0	26.1	22.7	21.8	22.9	20.1	25.0	12.5	7.9	17.7	12.2	16.9	16.6
Unspecified lymphomas (IIe subgroup)	2.1	0.1	4.7	1.1	3.5	0.0	1.1	0.0	2.8	2.7	0.0	0.0	1.8	0.7	3.9	2.3	1.9

SEE Southern and Eastern Europe, *SEER* Surveillance, Epidemiology and End Results, ICCC-3: International Classification of Childhood Cancer, *HL* Hodgkin's lymphoma, *NHL* non-Hodgkin lymphomas, *BL* Burkitt lymphoma

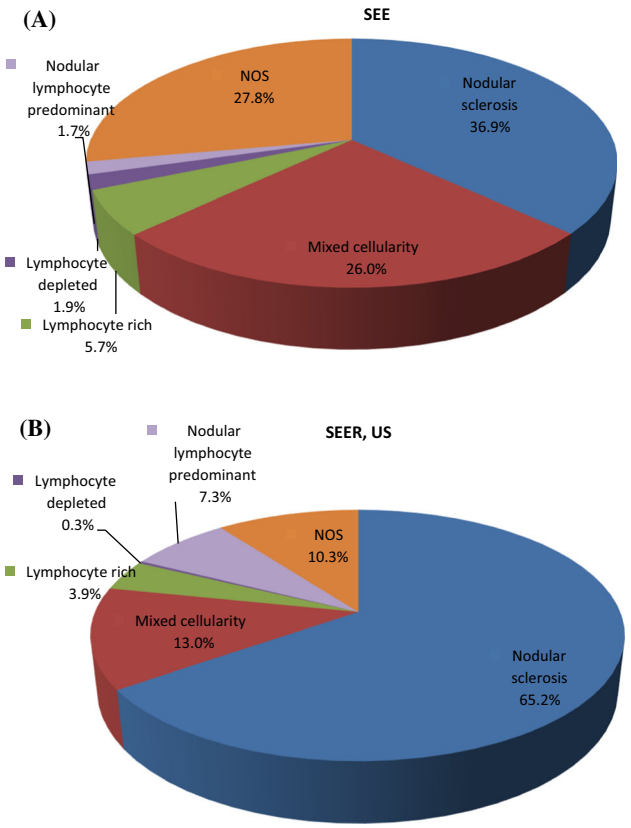

Fig. 1 Distribution of Hodgkin lymphoma cases by histological subtypes in **a** Southern and Eastern European (SEE) registries overall ($n = 2{,}191$; 1990–2014) and **b** the Surveillance and Epidemiology End Results (SEER), USA ($n = 1{,}733$; 1990–2012). *NOS* not otherwise specified. (Color figure online)

differences by age were observed for HL with a higher male preponderance in the younger age groups and male/female ratios of crude incidence rates: 3.1, 2.7, and 1.1 in the three age groups, respectively. On the contrary, for NHL and BL the lowest male/female ratio was recorded in the age group 0–4 compared to the older ones (NHL: 1.6, 2.1, 1.9, BL: 3.0, 4.5, 4.2, respectively). As shown in Fig. 2, incidence rates increased with age for HL and NHL in both SEE registries and SEER. Unlike SEER, however, where this increase followed a rather linear pattern for both genders, in SEE registries an incidence peak at 4 years, more prominent in males, was also documented for HL. Regarding NHL, an abrupt incidence increase in age until 5 years, especially for males, was noted in SEE registries; in older children however, NHL rates remained rather stable by age in SEE, but continued increasing for SEER, resulting in a higher incidence in the older age group. As contrasted to HL and NHL, BL incidence was highest at 4 years of age, which was evident in both geographical regions, even though better pronounced in SEE registries and males.

Temporal trends

The annual percent changes (APC) of incidence rates for lymphomas by diagnostic subtype, gender, and registry are presented in Table 4, whereas Supplementary Figure S1 presents the results of the overall Joinpoint regression analysis by geographical region. Statistically significant decreasing overall trends—evident for both HL and NHL—were found in SEE (annually, −2.1 and −1.2 %, respectively), pertaining also to the majority of the largest registries, except for an increase of HL in central and Northern Portugal. By contrast, time trends for the time period 1990–2012 were increasing for childhood lymphomas in SEER (+0.7 %); specifically, NHL incidence statistically significantly increased by 1.1 % annually and HL incidence followed a marginally significant increasing trend (+0.8, 95 % CI 0.0, 1.6). On the contrary, statistically significant increasing trends for BL were observed in the largest SEE registries, whereas no significant annual change was noted in SEER.

When exploring time trends by gender (Supplementary Tables S1–S2, Supplementary Figures S2–S3), the overall increasing trend of HL in SEER was found to be male specific, as contrasted to the increasing pattern of NHL that was restricted to females. On the contrary, the decreasing trends of both HL and NHL, as well as the BL increase, noted in SEE were more prominent in males.

The Joinpoint regression analysis showed no breaks in time trends of the overall SEE and SEER analyses; among SEE registries, only the decreasing trend observed in Ukraine in overall lymphomas was principally attributed to a significant decrease during period 2000–2008, followed by a nonsignificant increase thereafter.

Discussion

Comparison of the epidemiologic patterns of childhood (0–14 years) lymphoma and its subtypes based on individual registry data derived from 14 South-Eastern European cancer registries operating in 12 countries and SEER, USA, showed significant variations in incidence and time trends. In a study period spanning from 1990 to 2014, lymphoma incidence was overall higher in the SEE area compared to SEER, mainly on account of the higher HL and BL incidence. The male preponderance was evident across all registries, although the male/female ratio varied by age group and lymphoma subtype reaching a high 4.5 among BL cases aged 5–9 years. The overall incidence increased significantly with age, but for boys diagnosed with HL in SEE countries, an early childhood peak was also documented; BL followed a nonlinear pattern peaking at 4 years, in both SEE registries and SEER. Of note are

Table 3 Age-standardized incidence rates (AIR) of childhood (0–14 years) lymphomas by histological type per 1,000,000 individuals and male to female ratio in the 14 participating Southern and Eastern Europe and the Surveillance, Epidemiology, and End Results (SEER), US

Registry (registration period)	All lymphomas[a]			Hodgkin lymphomas (ICCC-3, IIa subgroup)			Non-Hodgkin lymphomas-excluding Burkitt (ICCC-3, IIb subgroup)			Burkitt lymphomas (ICCC-3, IIc subgroup)		
	n	AIR	M:F ratio	*n*	AIR	M:F ratio	*n*	AIR	M:F ratio	*n*	AIR	M:F ratio
Southern and Eastern European countries												
Belarus (1990–2014)	833	17.7	2.1	440	8.9	1.6	194	4.3	2.3	198	4.5	4.3
Bulgaria (1990–2013)	530	16.7	2.2	264	8.2	2.4	192	6.1	1.8	49	1.7	3.6
Croatia (2001–2013)	177	18.4	2.0	73	7.3	1.7	77	8.3	2.0	25	2.7	4.2
Cyprus (1998–2011)	57	24.5	2.3	29	12.0	1.2	22	9.8	4.2	4	1.9	NA
Greece (1996–2014)	532	15.7	2.4	218	6.1	1.6	175	5.2	2.4	139	4.4	5.0
Izmir (1996–2012)	273	20.0	1.9	104	7.2	1.8	104	7.6	2.1	62	4.9	1.7
Malta (1996–2013)	23	16.6	3.7	9	6.1	6.8	9	6.8	1.5	5	3.8	NA
Portugal Central (1990–2010)	144	16.9	1.9	74	8.1	1.4	33	3.9	2.3	33	4.5	2.6
Portugal North (1995–2010)	189	20.4	1.7	80	7.9	1.2	66	7.6	2.4	38	4.4	2.2
Romania-Cluj (2006–2011)	28	10.7	2.1	11	4.1	5.0	10	3.8	0.9	7	2.8	2.6
Romania Northeast (2008–2010)	24	11.7	1.5	10	4.6	0.9	11	5.6	2.4	3	1.5	1.2
Serbia (2000–2011)	166	15.7	1.6	58	5.3	1.7	92	9.0	1.5	13	1.2	5.3
Slovenia (1990–2011)	147	19.0	2.4	61	7.4	1.6	59	7.7	2.7	26	3.7	5.0
Ukraine (2000–2012)	1,579	16.1	2.0	760	7.4	1.6	564	6.0	2.2	193	2.1	3.8
Overall SEE	4,702	16.9	2.0	2,191	7.5	1.6	1,608	5.9	2.1	795	3.1	3.6
SEER (1990–2012)	4,416	13.6	1.8	1,733	5.1	1.4	1,867	5.8	1.7	731	2.3	4.1
Total	9,118	15.1	1.9	43.0	6.2	1.6	38.1	5.9	1.9	16.8	2.7	3.8

ICCC-3 International Classification of Childhood Cancer, *AIR* age-standardized incidence rates, *M:F ratio* male to female ratio of age-standardized incidence rates

[a] Lymphomas include cases of ICCC-3 diagnostic subtypes IIa (Hodgkin's lymphomas), IIb (non-Hodgkin lymphomas–excluding Burkitt lymphomas), IIc (Burkitt lymphomas) and IIe (unspecified lymphomas)

also the decreasing temporal trends of HL and NHL, in SEE registries, mostly prominent for males, as contrasted to the increasing male-specific HL and female-specific NHL pattern in the USA. Lastly, an increasing incidence time trend was also recorded for BL male cases in SEE.

Cross-country variation by lymphoma subtype

Regarding HL, our findings are in line with those derived from previously published studies reporting similar incidence rates of $6.8/10^6$ in Southern and $8.0/10^6$ in Eastern European countries, minimally overlapping with the present dataset, whereas the rates from the Western ($5.8/10^6$), Northern Europe ($4.5/10^6$), the UK ($4.3/10^6$), and Canada ($5.5/10^6$) [24] were lower and closer to those of SEER; interestingly, Italy seems to have the highest HL incidence worldwide among children and adolescents (0–19 years), according to a recent report [26]. Higher incidence rates have been also reported in the less developed countries of Latin America and Asia [9], possibly reflecting socioeconomic development disparities [19]. Notably, 4 (Belarus, Serbia, Turkey, and Ukraine) out of the 12 registries, accounting for 61 % of the total SEE lymphoma cases, are not included in those with developed economies according to the 2016 United Nations report [34]; moreover, during the early 90s when cancer registration was initiated in most of the participating registries, only Greece and Portugal were considered developed.

The HL geographical incidence disparities seem to widen with decreasing age, mainly among males, in this dataset. Accumulating epidemiologic evidence supports that a childhood HL entity, distinct from that diagnosed during adolescence and young adulthood may exist, as was firstly described 50 years ago by MacMahon [35]. A more recent report from Nordic registries showed differential epidemiologic characteristics for HL in the age groups 0–6 and 7–14 years, supporting the existence of two separate entities in the overall childhood category [36]. The childhood entity has been conventionally interpreted in the context of socioeconomic deprivation of the population under study [35, 37]; as a matter of fact, the age-specific incidence rates for HL are dissimilar across the world, with the incidence in sub-Saharan Africa countries and Egypt peaking in the younger age group [26]. However, the age-specific HL

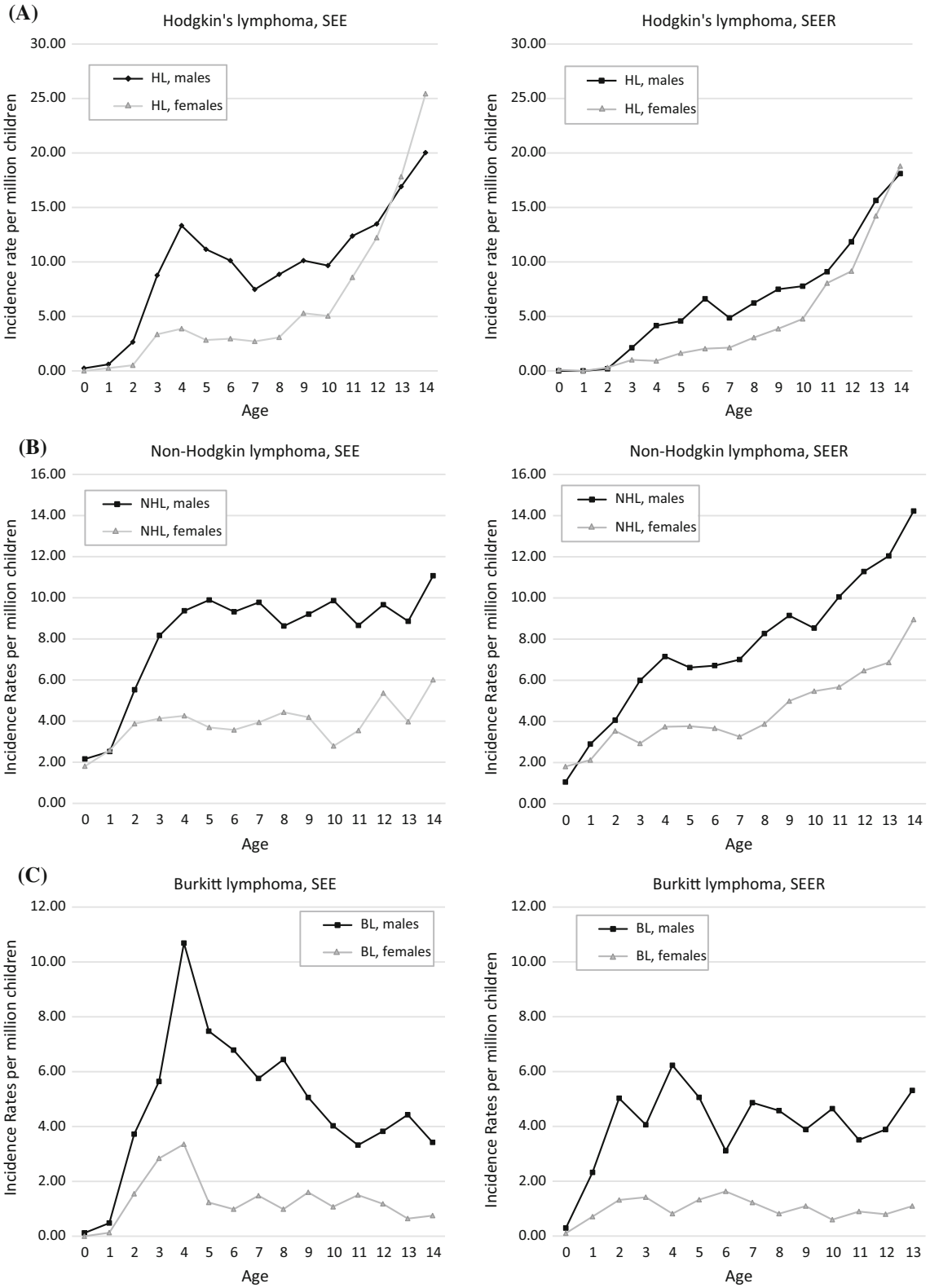

Fig. 2 Crude incidence rates per million children of childhood **a** Hodgkin's lymphoma (HL), **b** non-Hodgkin lymphoma-excluding Burkitt, and **c** Burkitt lymphoma (BL) by age and gender between Southern and Eastern European registries overall (1990–2014; *left panel*) and the Surveillance and Epidemiology End Results, USA (1990–2012; *right panel*)

Table 4 Annual percent change (APC)[a] and 95 % confidence intervals (95 % CIs) derived from Poisson regression analysis for childhood (0–14 years) lymphomas by diagnostic subtype and gender in the 14 participating Southern and Eastern European (SEE) registries and the Surveillance, Epidemiology, and End Results (SEER), USA

Country	All lymphomas[b]				Hodgkin lymphomas (ICCC-3, IIa subgroup)				Non-Hodgkin lymphomas-excluding Burkitt (ICCC-3, IIb subgroup)				Burkitt lymphomas (ICCC-3, IIc subgroup)			
	APC	95 % CI		*p* value	APC	95 % CI		*p* value	APC	95 % CI		*p* value	APC	95 % CI		*p* value
Belarus (1990–2014)	**−2.5**	**−3.4**	**−1.5**	**<0.001**	**−3.1**	**−4.4**	**−1.7**	**<0.001**	**−2.2**	**−4.2**	**−0.2**	**0.03**	−1.5	−3.4	0.5	0.14
Bulgaria (1990–2013)	−0.2	−1.4	1.0	0.72	−0.3	−2.0	1.5	0.75	−0.8	−2.8	1.3	0.46	**7.8**	**3.4**	**12.3**	**<0.001**
Croatia (2001–2013)	−0.1	−4.0	3.9	0.95	**−6.1**	**−11.8**	**0.0**	**0.05**	1.3	−4.6	7.5	0.68	**15.2**	**3.0**	**28.8**	**0.01**
Greece (1996–2014)	−0.3	−1.8	1.3	0.74	−0.8	−3.2	1.6	0.51	−1.3	−3.9	1.4	0.35	1.9	−1.1	5.0	0.22
Izmir (1996–2012)	0.9	−1.5	3.4	0.46	2.9	−1.1	7.0	0.16	−1.4	−5.2	2.5	0.47	1.2	−3.8	6.4	0.65
Portugal central (1990–2010)	**3.7**	**1.0**	**6.6**	**0.008**	**4.4**	**0.5**	**8.4**	**0.03**	0.8	−4.6	6.6	0.77	4.2	−1.5	10.2	0.15
Portugal north (1995–2010)	1.1	−2.0	4.3	0.48	4.3	−0.6	9.4	0.09	**−6.3**	**−11.3**	**1.1**	**0.02**	**8.7**	**1.2**	**16.8**	**0.02**
Serbia (2000–2011)	**−9.1**	**−13.2**	**−4.8**	**<0.001**	**−13.0**	**−19.7**	**−5.7**	**0.001**	**−8.5**	**−13.9**	**−2.7**	**0.005**	1.4	−13.4	18.6	0.87
Slovenia (1990–2011)	0.9	−1.6	3.5	0.48	0.9	−3.0	4.9	0.66	−1.1	−5.0	3.0	0.60	6.0	−0.3	12.6	0.06
Ukraine (2000–2012)	**−3.2**	**−4.5**	**−1.9**	**<0.001**	**−5.2**	**−7.0**	**−3.3**	**<0.001**	**−4.2**	**−6.3**	**−2.1**	**<0.001**	**11.6**	**7.4**	**15.9**	**<0.001**
SEE (1990–2012)	**−1.3**	**−1.8**	**−0.8**	**<0.001**	**−2.1**	**−2.8**	**−1.4**	**<0.001**	**−1.2**	**−2.1**	**−0.4**	**0.004**	1.3	0.0	2.5	0.05
SEER (1990–2012)	**0.7**	**0.2**	**1.2**	**0.008**	0.8	0.0	1.6	0.07	**1.1**	**0.4**	**1.9**	**0.004**	0.5	−0.7	1.7	0.42

Bold indicates statistical significance (p value < 0.05)

ICCC-3 International Classification of Childhood Cancer

[a] APC was not calculated for Cyprus, Malta, and the two Romanian registries, due to the small number of cases and limited available study periods

[b] Lymphomas include cases of ICCC-3 diagnostic subtypes IIa (Hodgkin's lymphomas), IIb (non-Hodgkin lymphomas-excluding Burkitt lymphomas), IIc (Burkitt lymphomas), and IIe (unspecified lymphomas)

entities may also differ on the basis of their association with EBV infection [6–8, 38]. According to the findings of a large meta-analysis, EBV-positive HL is usually more common in Africa, South/Central America, and Asia, compared to Europe and Northern American countries, among pediatric cases, compared to younger adults, and among males, whereas it is more closely related to the mixed cellularity and the lymphocyte-depleted subtypes; on the contrary, the EBV-negative subtype, not gender specific, is pathologically more commonly expressed as nodular sclerosis [38, 39]. The higher prevalence of the mixed cellularity subtype and the age peak in early childhood, especially among males recorded in the SEE registries vs. that of SEER, are in accordance with previous studies [10, 40, 41] supporting the notion that the geographical differences could be attributed to the EBV-related HL patterns. Whether EBV infection is the primary and unique cause of this discrepancy or other environmental causes lead to the observed EBV-positive and EBV-negative associations, needs to be further explored [20, 21]. Although the world prevalence of EBV infection is estimated at 95 %, EBV exposure occurs later in the developed countries [42]. This observation could generate speculations regarding the timing of infection exposure and the maturity of the immune system on lymphoma pathogenesis [22]. It should be noted though that the association of socioeconomic deprivation, early exposure to infections, and lymphomagenesis have not been replicated in all studies [43, 44].

The overall childhood NHL incidence rate in SEE countries ($5.9/10^6$) was similar to SEER and comparable to overall rates reported by a previous study in the European region [25], showing a higher incidence ($7.3/10^6$) in Western and a lower in Northern ($4.8/10^6$) European countries [25]. On the contrary, the incidence of BL in the SEE registries ($3.1/10^6$) was higher than SEER ($2.3/10^6$). Interestingly, considerable incidence variations were observed in NHL and BL subtypes between SEE registries. Overall, registries with low BL incidence reported higher NHL rates, pointing to potential misclassification of the BL cases in the NHL category; this assumption is supported by the high percentage of NHL NOS cases in SEE ($\sim$40 %) as contrasted to $<$10 % in SEER. This misclassification may be due to the non-use of specific diagnostic methods, especially in the early registration years in the less developed Eastern countries. However, it would be expected that a more accurate NHL-BL classification would widen the difference in BL incidence between SEE and SEER. Indeed, BL incidence was twice as high in Belarus and Greece, two relatively large SEE registries with high MV percentage, compared to the SEER database [45]. A previous study including four continents, except for Africa, reported an age-adjusted incidence rate of $\sim$2 per million children in the Central and Western Europe, Canada, and Australia, and a higher rate in Asian countries in the age group 0–19 years [46]. Infectious agents are also implicated in the pathogenesis of NHL [47, 48], but for both HL and NHL, between-registry differences in incidence could imply diverse genetic predisposition, given the ethnic origins disparities between participating countries [49–51].

The male preponderance by a factor of two overall and the increasing incidence in developed countries of total lymphomas by age, apart from BL, were replicated in this large dataset [52–54]. On the contrary, the distribution of BL by age was nonlinear peaking at 4 years. A childhood peak has been previously described in other studies along with consequent peaks in adulthood, one in 40 and another one in 70 years [46, 55] possibly indicating different underlying etiologies and representing biologically distinct entities [56]. The epidemiologic features of BL observed in our dataset seem to be mostly of the sporadic form rather than the endemic-African or the immunodeficiency-associated subtypes with a threefold to fourfold higher incidence among males [46, 57–59].

International discrepancies in descriptive epidemiology of childhood lymphoma should definitely be discussed in view of the potential under-ascertainment of cases, especially by recently initiated registries that may have not developed an extensive network for complete registration. In this context, it would be expected that an underestimation of childhood lymphoma incidence would be more likely in the SEE registries or registry-based studies from developing countries, compared to SEER and other large databases in developed countries with long registration history and high quality standards. Nevertheless, if this stipulation were genuine, it would be expected that the observed differences regarding HL and BL incidence between the SEE area and SEER would be even more prominent, whereas possibly a difference could also emerge for NHL.

Temporal comparisons by lymphoma subtype

Marginally increasing HL time trends in SEER and the two Portuguese registries are in line with the increasing trends also reported over the last two decades for Western European countries [12, 26, 60–62]. By contrast, decreasing trends were observed in four Eastern European registries (Belarus, Croatia, Ukraine, and Serbia) and SEE overall; it would be worthy to further explore whether these trends evidence a decrease in incidence of the mixed cellularity subtype in younger males, as a consequence of the socioeconomic development of the population, as has been previously reported for other countries [36, 40]. Similarly, it would be intriguing to investigate whether nodular sclerosis, has genuinely increased in SEER and what the underlying environmental factors might be. A UK study has reported a specific increase for the nodular sclerosis incidence, during 1954–1998 [62, 63], but such observations

should be interpreted in view of the difficulties in accurately classifying HL [64].

The reasons for the decreasing trends of NHL in SEE registries (Belarus, North Portugal, Serbia, Ukraine) may be country-specific and should be interpreted along with the respective increasing BL trends in the context of possible improvements in disease classification. Merging the NHL with BL incidence rates almost eliminated any significant trends in SEE, except for an overall decrease in Belarus and Serbia. Nevertheless, the role of abrupt environmental conditions such as the Yugoslavian war in the 1990s in Serbia and Croatia and the Chernobyl accident in Ukraine and Belarus leading to a higher incidence in early registration years is rather arbitrary and should be carefully documented [65–67]. By contrast, SEER data showed a significantly increasing annual NHL trend following similar findings previously reported for adults [68] and linked to advances in diagnostic procedures [69] and the HIV epidemic [70]. Exposures to environmental factors might underline the NHL increase, as well as the constant increase in the incidence of childhood acute lymphoblastic leukemia, an entity closer to NHL rather than other lymphoma types [70–72]. This female-specific increase, as contrasted to the male-specific increase for HL, merits further research.

Strengths and limitations

Although all SEE registries were characterized by a low proportion of DCOs and histologically unspecified cases, only seven of them reported high proportion of MVs (>90 %). Furthermore, improvements in registration methodologies over time might partially explain the observed increasing time trends in some SEE registries. Cross-registry variations in terms of study period, sample size, and country sociodemographic characteristics should be considered when interpreting comparisons between SEE countries and SEER. Lastly, the high proportion of HL and NHL NOS cases in SEE did not allow further exploration by specific morphological subtypes across countries and over the specified study period. On the positive side, strengths of this study entail its large total size for analysis of primary data on childhood lymphoma, allowing subanalyses by major diagnostic subtypes, age and gender, as well as comparisons between two areas of the world with diverse ethnic, cultural, financial, and environmental characteristics leading to the identification of certain geographical patterns and time trends.

Conclusions

In conclusion, for the first time registration data for childhood lymphoma from South-Eastern European countries, compared to the publicly available raw data of SEER, USA, show decreasing incidence trends of HL and NHL among SEE registries as contrasted to increasing trends in the USA, along with age and gender discrepancies. The diverse geographical patterns observed between SEE and USA could reflect divergence of the socioeconomic development levels of the underlying populations indicating environmental factors on the pathogenesis of disease. Optimization of cancer registration could allow further examination of more specific morphological subtypes and their tentative association with environmental factors including the role of certain infectious agents on immunity development and lymphomagenesis.

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Compliance with ethical standards

Conflict of interest None declared.

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