Long-term survival for lymphoid neoplasms and national health expenditure (EUROCARE-6): a retrospective, population-based study

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Summary

Background Management of lymphoid malignancies requires substantial health system resources. Total national health expenditure might influence population-based lymphoid malignancy survival. We studied the long-term survival of patients with 12 lymphoid malignancy types and examined whether different levels of national health expenditure might explain differences in lymphoid malignancy prognosis between European countries and regions.

Methods For this observational, retrospective, population-based study, we analysed the EUROCARE-6 dataset of patients aged 15 or older diagnosed between 2001 and 2013 with one of 12 lymphoid malignancies defined according to International Classification of Disease for Oncology (third edition) and WHO classification, and followed up to 2014 (Jan 1, 2001–Dec 31, 2014). Countries were classified according to their mean total national health expenditure quartile in 2001–13. For each lymphoid malignancy, 5-year and 10-year age-standardised relative survival (ASRS) was calculated using the period approach. Generalised linear models indicated the effects of age at diagnosis, gender, and total national health expenditure on the relative excess risk of death (RER).

Findings 82 cancer registries (61 regional and 21 national) from 27 European countries provided data eligible for 10-year survival estimates comprising 890 730 lymphoid malignancy cases diagnosed in 2001–13. Median follow-up time was 13 years (IQR 13–14). Of the 12 lymphoid malignancies, the 10-year ASRS in Europe was highest for hairy cell leukaemia (82·6% [95% CI 78·9–86·5) and Hodgkin lymphoma (79·3% [78·6–79·9]) and lowest for plasma cell neoplasms (29·5% [28·9–30·0]). RER increased with age at diagnosis, particularly from 55–64 years to 75 years or older, for all lymphoid malignancies. Women had higher ASRS than men for all lymphoid malignancies, except for precursor B, T, or natural killer cell, or not-otherwise specified lymphoblastic lymphoma or leukaemia. 10-year ASRS for each lymphoid malignancy was higher (and the RER lower) in countries in the highest national health expenditure quartile than in countries in the lowest quartile, with a decreasing pattern through quartiles for many lymphoid malignancies. 10-year ASRS for non-Hodgkin lymphoma, the most representative class for lymphoid malignancies based on the number of incident cases, was 59·3% (95% CI 58·7–60·0) in the first quartile, 57·6% (55·2–58·7) in the second quartile, 55·4% (54·3–56·5) in the third quartile, and 44·7% (43·6–45·8) in the fourth quartile; with reference to the European mean, the RER was 0·80 (95% CI 0·79–0·82) in the first, 0·91 (0·90–0·93) in the second, 0·94 (0·92–0·96) in the third, and 1·45 (1·42–1·48) in the fourth quartiles.

Interpretation Total national health expenditure is associated with geographical inequalities in lymphoid malignancy prognosis. Policy decisions on allocating economic resources and implementing evidence-based models of care are needed to reduce these differences.

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Introduction

Haematological malignancies account for approximately 7% of all cancers worldwide[1] and more than half are lymphoid malignancies. In 2020, the age-standardised incidence rates (per 100 000) in Europe for both genders were estimated as 16·4 for non-Hodgkin lymphoma, 6·8 for multiple myeloma, and 2·7 for Hodgkin lymphoma.[2] The incidence of lymphoid malignancies is higher in men than in women and increases with age,[2] typically affecting older people.[3]

The improvements in survival reported by the EUROCARE-5 study for many lymphoid malignancies coincided with the introduction of new treatments, such as anti-CD20 monoclonal antibodies for treating B-cell lymphomas and acute lymphoblastic leukaemia or proteasome inhibitors for multiple myeloma.[4] The development of chimeric antigen receptor redirected

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See Online for appendix

Research in context

Evidence before this study

Cancer registry-based survival studies on lymphoid malignancies usually provide 5-year survival estimates, whereas long-term survival is available for specific malignancy types or on a national basis only. The improvements in 5-year survival reported by previous EUROCARE studies for many lymphoid malignancies coincided with the introduction of new treatments but persisting survival differences across Europe suggest inequalities in quality of care and access to treatments exist. Total national expenditure on health—an indicator of a country's overall investment in its health system—was associated with 5-year all-cancer survival, but its influence on long-term survival for specific lymphoid malignancies has not been investigated. No formal literature review was done before the start of the study.

Added value of this study

To our knowledge, this is the first study to provide 10-year survival estimates for 12 specific lymphoid malignancies in 27 European countries, using data from 82 population-based cancer registries. It is also the first study to systematically analyse the relationship between survival for each lymphoid malignancy and total national health expenditure. For all the lymphoid malignancies, 5-year and 10-year age-standardised relative survival (ASRS) in countries in the highest total national health expenditure quartile was higher than in countries in the lowest quartile, with a gradual decrease in survival through decreasing expenditure quartiles, although this pattern differed by lymphoid malignancy subgroup. For common lymphoid malignancies, such as Hodgkin lymphoma and non-Hodgkin lymphoma, survival was similar across the countries in the high and medium-high quartiles. 10-year ASRS for Hodgkin lymphoma decreased from the highest to lowest quartile. The decrease through quartiles was less uniform for lymphoid malignancies with poor prognosis, such as mantle cell lymphoma. In most countries in the first or second total national health expenditure quartiles, 10-year ASRS was in line with or above the European mean for common lymphoid malignancies. Exceptions were England, Scotland, Northern Ireland, Finland, and Austria, where survival for some lymphoid malignancies was lower than the European mean. Multivariable survival models (adjusted by age, gender, and total national health expenditure), applied for each lymphoid malignancy, confirmed that 10-year survival was better in countries with higher health-care expenditure than in those with lower expenditures.

Implications of all the evidence

In countries with low total national health expenditure, policy decisions are needed to increase health-care resources and identify strategies to sustain interventions. Differences in lymphoid malignancy survival among countries with similar total national health expenditure indicate the need to investigate national health-care policies and health resource utilisation. All these countries need to implement efficient, evidence-based care and long-term surveillance to reduce inequalities. Given the high cost of drugs for haematological malignancies, political pressure and negotiations with drug manufacturers to reduce the prices of the most expensive drugs should be pursued.

T-cell (CAR-T) therapy[5] and other therapeutic targets (eg, BTK inhibitors) is expected to improve survival for patients with various B-cell neoplasms.[6] However, persistent survival inequalities across Europe suggest differences in quality of care and access to treatments exist.[7]

The high and increasing costs of lymphoid malignancy management—due to expensive drugs, complex regimens, and the need for extensive support services and after-care surveillance—require substantial health system resources.[8] Total national expenditure on health was associated with 5-year all-cancer survival in the EUROCARE-5 study,[9] but its association with long-term survival for specific lymphoid malignancies has not been investigated.

As increasing numbers of patients with haematological malignancies in Europe survive for more than 5 years after their initial diagnosis,[10,11] survival needs to be analysed beyond the conventional 5-year timeframe usually reported. Studies investigating long-term survival indicated that follicular lymphoma[12,13] survival continues to decrease over the follow-up years and mortality remained higher than in the general population even 10 years after diagnosis.[10] Studies in children and adolescents reported that the persisting excess risk of death[14] might be attributable to secondary cancers, late relapses of non-Hodgkin lymphoma, or cardiovascular disease.[15]

Apart from late relapses, the excess mortality of patients with lymphoid malignancies, persisting for more than 5 years after diagnosis, has also been attributed to the long-term adverse effects of cytotoxic therapy,[16] multimorbidity,[17] and social deprivation.[18]

Total national health expenditure represents the country's general resources for health, allowing us to evaluate how the economic availabilities can contribute to differences in health outcomes and permitting reliable results comparison among countries. It is a sufficiently standardised macroeconomic indicator collected by national and international statistics offices. Total national health expenditure has already been considered for evaluating differences in non-Hodgkin lymphoma survival across countries.[19] It is a general descriptor that is useful to uncover potential issues to be better explored by future studies, outside the EUROCARE-6 framework.

We studied the long-term survival of patients with 12 specific lymphoid malignancy types and examined whether different levels of total national health expenditure might explain differences in lymphoid malignancy prognosis between European countries and regions.

Methods

Study design and data collection

For this observational, retrospective, population-based study, we selected 10-year survival data of adults (aged ≥15 years) diagnosed with lymphoid malignancies from the dataset of the EUROCARE-6 study, which relies on standardised information provided by population-based cancer registries in Europe. The quality and completeness of cancer registry data were assessed with standardised EUROCARE and European Network of Cancer Registries and Joint Research Centre checking procedures.[20] The study protocol is available online.

Morphology was coded according to the International Classification of Disease for Oncology, third edition (ICDO-3),[21] and 2017 WHO classification (WHO-4),[22] with some updates introduced in the 2023 revision. We collected data on date of birth, diagnosis, and death, vital status, and gender through patients' medical records held at cancer registries.

The lymphoid malignancy types analysed were Hodgkin lymphoma, the group of non-Hodgkin lymphoma, and ten specific types: chronic lymphocytic leukaemia/small lymphocytic lymphoma; lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia; diffuse large B-cell lymphoma; mantle cell lymphoma; follicular lymphoma; marginal zone lymphoma; mature T and natural killer cell lymphoma; precursor B-cell, T-cell, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia; plasma cell neoplasms; and hairy cell leukaemia. Detailed ICDO morphology codes of the lymphoid malignancy forms analysed with their acronyms are provided in the appendix (p 13).

Statistical analysis

We computed relative survival (the cancer-specific survival probability) with the Ederer II method, using SEER*Stat software and registry-specific lifetables stratified by age, gender, and year. 5-year and 10-year relative survival in the follow-up period (2010–14; selecting patients diagnosed in 2001–13), with 95% CIs, were calculated by country, gender, and age at diagnosis using the period approach, which provides the most up-to-date estimates of the survival of patients diagnosed in 2010–14.[23] In our analyses, the Ederer II estimator was less prone than the net survival estimator to estimates' instabilities or increases for long follow-up durations that typically occur with scarce number of cases and in older age groups.[24] Relative survival SEs were calculated with Greenwood's formula assuming fixed expected survival. Two-sided 95% CIs were computed using logarithmic transformation.

Age at diagnosis was divided into five groups (15–44, 45–54, 55–64, 65–74, and ≥75 years) and reduced to four for Hodgkin lymphoma and precursor B-cell, T-cell, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia (15–44, 45–54, 55–64, and ≥65 years) and for mantle cell lymphoma and marginal zone lymphoma (15–54, 55–64, 65–74, and ≥75 years).

To account for different age structures of European populations, country-specific relative survival estimates were standardised by age with international cancer survival standards.[25] European mean survival was computed by weighting area-specific survival by the population of each area (northern, central, southern, and eastern Europe; UK; and Ireland).

The total national health expenditure—in US$ purchasing power parity per capita—by country was determined annually for 2001–13 from key international databases (eg, Health for All Europe, Organisation for Economic Co-operation and Development, World Bank Database, and local national statistics offices).

Countries were scored according to their mean total national health expenditure in 2001–13 and divided into quartiles of expenditure (low, middle-low, middle-high, and high). We adopted total national health expenditure quartiles for easier interpretation of results, while accepting the loss of some precision and leaving for future analyses the application of more structured methods (ie, fractional polynomial or regression spline scales). Reliability and standardisation of total national health expenditure data made this choice reasonable.

The I^2 statistic was calculated to establish the percentage of total between-country survival differences due to heterogeneity rather than chance.[26] The higher the I^2 statistic, the more the differences are due to true heterogeneity between the populations.

Generalised linear models were used in multivariable regressions to assess the effects of age at diagnosis, gender, and total national health expenditure on the relative excess risks of death (RERs), with 95% CIs, for each lymphoid malignancy group in the 10 years after diagnosis. The selection of the variables was determined by their availability in cancer registry databases. We used a Poisson regression model, in which the response variable was the difference between observed and estimated deaths and the predictors were age at diagnosis (grouped as described earlier), gender, and total national health expenditure in quartiles (grouped as above; appendix p 26).[27]

The possible combined effects of age, gender, and total national health expenditure on RERs were investigated. After considering only the main effects, generalised linear models with both two-way and three-way interaction effects along with the main effects were computed.[28] Given the high number of cases, Hodgkin lymphoma and non-Hodgkin lymphoma groups were considered for examining possible association between total national health expenditure and RERs in subgroups

For more on the **EUROCARE-6 data** see https://encr.eu/sites/default/files/Data_call/2015_ENCR_JRC_Call_for_Data_Version_1_1.pdf

For the **study protocol** see https://www.iss.it/en/eurocare-6

For more on the **morphology coding** see https://seer.cancer.gov/tools/heme/

For the **health data from the Organisation for Economic Co-operation and Development** see https://www.oecd.org/els/health-systems/health-data.htm

For the **SEER*Stat software** see https://seer.cancer.gov/seerstat/

defined by age (15–54 and 55+ years) and gender.[29] The computation of RERs by generalised linear model were repeated for these subgroups.

Data were analysed using SEER*Stat software (version 8.3.9), SAS (version 9.4), and STATA (version 17.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 913 244 eligible lymphoid malignancy cases diagnosed in 27 European countries between 2001 and 2013 (table 1), 1956 (0·2%) were excluded because of major errors (missing or invalid data and inconsistencies in essential variables to compute survival, such as dates, information on vital status, basis of diagnosis, topography, and morphology). Moreover, 16 921 (1·9%) cases known only from death certificates and 2396 (0·3%) incidentally detected at autopsy were also excluded. The proportions of cases known only from death certificates were relatively high in Germany, Austria, Bulgaria, and Slovakia (table 1).

The number of cases alive with unknown survival time was 1239 (0·1%); the number of cases lost to follow-up (ie, censored alive before the follow-up closing date) 624 (0·5%) at 5 years, with the highest proportions in

	All lymphoid malignancy cases, 2001–13	Invalid cases excluded from survival analysis, n (%)				Data quality indicator, n (%)	
		Major errors	Death certificate only	Incidentally detected at autopsy	Alive cases with unknown survival time	Lost to follow-up*	NOS morphology†
Austria	27 330	0	1703 (6·2%)	0	0	0	4746 (18·5%)
Bulgaria	13 840	24 (0·2%)	730 (5·3%)	0	0	0	2514 (19·2%)
Croatia	11 877	0	0	0	78 (0·7%)	0	3230 (27·4%)
Czechia	34 289	20 (0·1%)	281 (0·8%)	1546 (4·5%)	172 (0·5%)	0	4770 (14·8%)
Denmark	24 363	36 (0·1%)	0	35 (0·1%)	2 (<0·1%)	15 (0·5%)	1588 (6·5%)
Estonia	4035	0	61 (1·5%)	50 (1·2%)	0	4 (0·9%)	297 (7·6%)
Finland	24 465	614 (2·5%)	2 (<0·1%)	13 (0·1%)	0	0	4324 (18·1%)
France (13 cancer registries)	53 792	0	0	0	101 (0·2%)	83 (1·0%)	2503 (4·7%)
Germany (5 cancer registries)	76 666	41 (0·1%)	6334 (8·3%)	23 (<0·1%)	111 (0·1%)	77 (0·9%)	6181 (8·8%)
Iceland	1128	0	3 (0·3%)	7 (0·6%)	0	0	30 (2·7%)
Ireland	14 649	1 (<0·1%)	73 (0·5%)	58 (0·4%)	0	0	2210 (15·2%)
Italy (29 cancer registries)	93 602	10 (<0·1%)	484 (0·5%)	136 (0·1%)	199 (0·2%)	290 (1·9%)	10 583 (11·4%)
Latvia	5153	7 (0·1%)	1 (<0·1%)	0	0	0	587 (11·4%)
Lithuania	9295	0	54 (0·6%)	6 (0·1%)	11 (0·1%)	15 (1·4%)	653 (7·1%)
Malta	1341	2 (0·1%)	1 (0·1%)	21 (1·6%)	0	0	194 (14·7%)
Netherlands	68 531	514 (0·8%)	0	203 (0·3%)	0	0	1386 (2·0%)
Norway	21 934	294 (1·3%)	120 (0·5%)	5 (<0·1%)	0	0	994 (4·6%)
Poland	81 286	90 (0·1%)	1457 (1·8%)	48 (0·1%)	475 (0·6%)	0	24 340 (30·7%)
Portugal (2 cancer registries)	23 245	56 (0·2%)	8 (<0·1%)	0	58 (0·2%)	44 (1·2%)	5342 (23·1%)
Slovakia	11 753	4 (<0·1%)	605 (5·1%)	46 (0·4%)	0	0	399 (3·6%)
Slovenia	6556	0	0	83 (1·3%)	1 (<0·1%)	0	283 (4·4%)
Spain (8 cancer registries)	29 115	116 (0·4%)	244 (0·8%)	54 (0·2%)	5 (<0·1%)	17 (0·3%)	1414 (4·9%)
Switzerland (4 cancer registries)	7196	0	27 (0·4%)	24 (0·3%)	26 (0·4%)	71 (5·8%)	297 (4·2%)
England (UK)	223 285	93 (<0·1%)	4339 (1·9%)	0	0	0	26 471 (12·1%)
Northern Ireland (UK)	7028	2 (<0·1%)	46 (0·7%)	8 (0·1%)	0	0	1013 (14·5%)
Scotland (UK)	24 250	2 (<0·1%)	62 (0·3%)	32 (0·1%)	0	8 (0·3%)	2042 (8·5%)
Wales (UK)	13 240	28 (0·2%)	286 (2·2%)	0	0	0	1461 (11·3%)
European pool (82 cancer registries)	913 244	1956 (0·2%)	16 921 (1·9%)	2396 (0·3%)	1239 (0·1%)	624 (0·5%)	109 852 (12·3%)

Data quality indicators are shown by country, with numbers of cases by specific malignancy. NOS=not otherwise specified. *Proportion of patients diagnosed in 2005–08, censored on Dec 31, 2013, with less than 5 years of follow-up; the proportion is calculated for cases diagnosed in 2005–07 in Croatia and Germany (two of five cancer registries), where follow-up closing date was Dec 31, 2012. †NOS International Classification of Disease for Oncology, third edition, morphology for lymphoid malignancies: 9590, 9591, 9820, 9832.

Table 1: **Data checks for adults (aged ≥15 years) diagnosed with lymphoid malignancy in 2001–13 in Europe**

	All lymphoid malignancies	Hodgkin lymphoma	Non-Hodgkin lymphoma	Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	Lymphoplasmacytic lymphoma/ Waldenström macroglobulinaemia	Diffuse large B-cell lymphoma	Mantle cell lymphoma	Follicular lymphoma	Marginal zone lymphoma	Mature T-cell and natural killer cell lymphoma	Precursor B-cell, T-cell, natural killer cell, or not-otherwise-specified lymphoblastic lymphoma/ leukaemia	Plasma cell neoplasms	Hairy cell leukaemia
Austria	25 627	1981	13 987	4478	567	3066	655	1956	926	1312	579	4748	330
Bulgaria	13 086	1868	6064	2541	187	1789	159	478	43	432	623	2187	184
Croatia	11 797	1293	5502	2221	108	864	72	875	73	137	415	2305	129
Czechia	32 270	3207	16 842	6864	366	5326	816	2495	663	1338	661	5099	294
Denmark	24 290	1671	12 688	5275	907	4640	666	2409	752	951	454	4425	253
Estonia	3924	390	1761	1040	49	751	113	119	94	130	107	739	40
Finland	23 836	1724	13 911	3791	NA	NA	NA	NA	NA	NA	443	4526	210
France (13 cancer registries)	53 691	3946	29 193	10 870	2966	8925	1392	4840	3205	3041	1039	9663	586
Germany (5 cancer registries)	70 157	4905	36 125	13 756	1731	11 697	1953	6479	2897	3530	1346	14 212	674
Iceland	1118	108	572	187	46	199	25	123	56	58	29	233	8
Ireland	14 517	1276	7524	2775	273	2163	245	1291	249	591	331	2786	175
Italy (29 cancer registries)	92 773	8260	50 418	13 742	2494	15 716	1821	6767	4515	4525	2217	20 142	1038
Latvia	5145	586	2104	1380	55	504	15	172	477	222	178	878	26
Lithuania	9224	862	3954	2633	108	1486	231	196	326	544	274	1749	72
Malta	1317	149	833	100	16	256	17	111	38	162	49	206	12
Netherlands	67 814	5056	37 983	11 570	2546	15 105	2169	6748	3183	3421	1372	13 446	782
Norway	21 515	1514	11 592	3358	1034	4103	561	2333	892	1070	429	4660	216
Poland	79 216	9855	33 615	17 513	540	279	5	3928	1165	1955	2441	16 194	587
Portugal (2 cancer registries)	23 123	2386	14 055	2414	336	3505	359	1808	782	1079	486	4148	176
Slovakia	11 098	1230	4642	2878	176	2016	214	662	229	379	355	2348	113
Slovenia	6472	539	3331	1158	128	1373	230	416	444	293	155	1304	58
Spain (8 cancer registries)	28 696	2751	15 655	4579	649	5288	660	3304	1612	1676	694	5469	200
Switzerland (4 cancer registries)	7119	654	3901	1295	209	1345	242	677	427	371	128	1277	93
England (UK)	218 853	16 411	117 442	36 358	5840	39 458	4655	20 217	6541	7998	3785	47 174	2078
Northern Ireland (UK)	6972	620	3805	1001	109	1096	83	837	144	278	115	1567	66
Scotland (UK)	24 154	1889	12 938	4022	691	4725	447	2472	925	1122	399	4972	169
Wales (UK)	12 926	854	6836	2532	310	2402	286	1147	401	430	195	2700	119
European pool (82 cancer registries)	890 730	75 985	467 273	160 331	22 441	138 077	18 091	72 860	31 059	37 045	19 299	179 157	8688

NA=not available

Table 2: **Number of adult (aged ≥15 years) cases of lymphoid malignancy, by specific malignancy, diagnosed in 2001–13 in Europe, included in survival analysis**

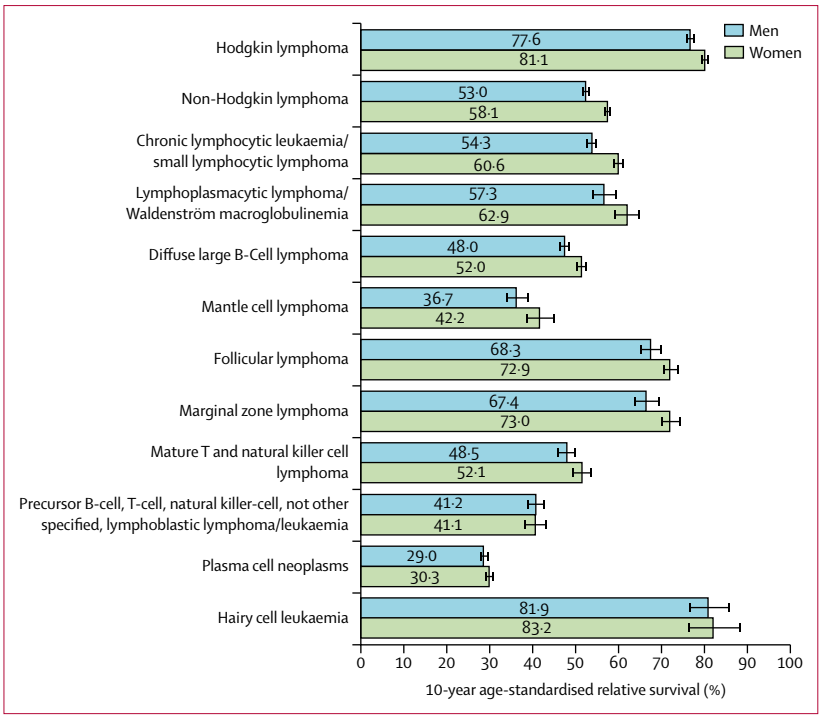


Figure 1: **10-year age-standardised relative survival for adult patients followed up in 2010–14 in Europe for each lymphoid malignancy**
Data are presented as percentages with 95% CIs indicated by error bars.

Switzerland and Italy (table 1). Cases lost to follow-up were not excluded from the analysis; they contributed for the whole period in which they were under observation, up to their censoring date. The percentages of not-otherwise-specified morphologies were higher in Poland, Croatia, Portugal, Bulgaria, Austria, and Finland than the European average (table 1).

Following these checks and exclusions, 890 730 lymphoid malignancy cases diagnosed in 2001–13 were included in the survival analysis (table 2). Results from the quality checks of cancer registry-specific data are shown in the appendix (pp 14–16). Of the 100 European cancer registries that submitted data, 82 registries (61 regional and 21 national) from 27 European countries provided data eligible for 10-year survival estimates—ie, data on adult cases diagnosed with lymphoid malignancies in 2001–13 and followed up until the end of 2014 (Jan 1, 2001, to Dec 31, 2014). Median follow-up time was 13 years (IQR 13–14). The categorisation of the countries on the basis of their total national health expenditure is shown in the appendix (pp 24–25).

Of the 12 lymphoid malignancies, the 10-year age-standardised relative survival (ASRS) in Europe was highest for hairy cell leukaemia (82·6% [95% CI 78·9–86·5]) and Hodgkin lymphoma (79·3% [78·6–79·9]) and lowest for plasma cell neoplasms (29·5% [28·9–30·0]). 10-year survival was similar for chronic lymphocytic leukaemia/small lymphocytic lymphoma (56·8% [56·1–57·5]) and non-Hodgkin lymphoma (55·3% [54·9–55·8]) with higher survival for the non-Hodgkin lymphoma types: follicular lymphoma (71·0% [69·6–72·4]) and marginal zone lymphoma (70·1% [68·4–71·9%]); survival was lower for diffuse large B-cell lymphoma (49·9% [49·2–50·7]) and mature T and natural killer cell lymphoma (49·9% [48·5–51·3]) and considerably lower for mantle cell lymphoma (37·9% [36·1–39·8]); lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia had an intermediate prognosis (59·4% [57·4–61·4]). Finally, precursor B, T, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia showed a poor prognosis (41·4% [39·9–42·9]; appendix pp 17–20).

Women generally had a better prognosis than men; the largest gender differences (5–6 percentage points) were for the whole non-Hodgkin lymphoma group and for the subtypes of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia, chronic lymphocytic leukaemia/small lymphocytic lymphoma, mantle cell lymphoma, and marginal zone lymphoma (figure 1).

For all lymphoid malignancies, relative survival decreased with older age (figure 2; appendix pp 2–7). For Hodgkin lymphoma, 10-year relative survival decreased from 92·3% (95% CI 91·8–92·8) in the youngest age class to 42·8% (40·4–45·4) in the oldest. 10-year relative survival was lowest for patients with precursor B, T, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia aged 65 years or older (11·8% [95% CI 9·7–14·3] compared with 56·1% [53·9–58·4] for the youngest group). For all lymphoid malignancies, age-specific relative survival was higher for women than men (data not shown).

The I^2 statistic (measuring heterogeneity not due to chance) was lowest for precursor B, T, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia (73·5%) and highest for non-Hodgkin lymphoma (98·2%), chronic lymphocytic leukaemia/small lymphocytic lymphoma (97·6%), and plasma cell neoplasms (93·8%; figure 3). For all other lymphoid malignancies, the I^2 exceeded 80%.

The largest European mean ASRS decrease from the 5th to the 10th year after diagnosis was around 16–19% for chronic lymphocytic leukaemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia, mantle cell lymphoma, and plasma cell neoplasms (appendix pp 17–20). There were smaller decreases (8–10%) for diffuse large B-cell lymphoma, follicular lymphoma, and marginal zone lymphoma, and for the whole non-Hodgkin lymphoma group. There were less marked differences (around 5–6%) for Hodgkin lymphoma, mature T and natural killer cell lymphoma, precursor B, T, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia, and hairy cell leukaemia.

For all the lymphoid malignancies, 5-year and 10-year ASRS in countries in the highest total national health expenditure quartile (high expenditure) was higher than

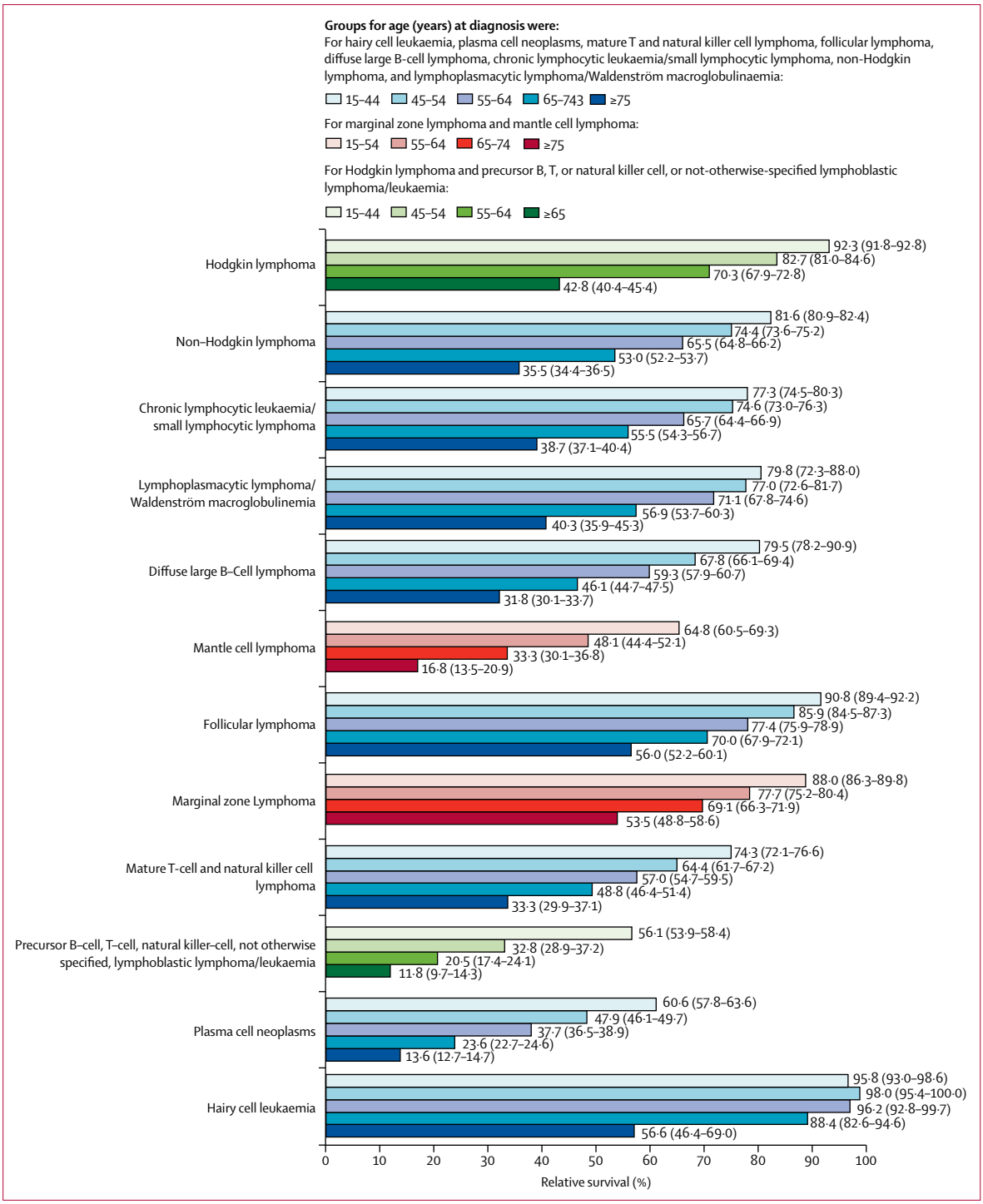
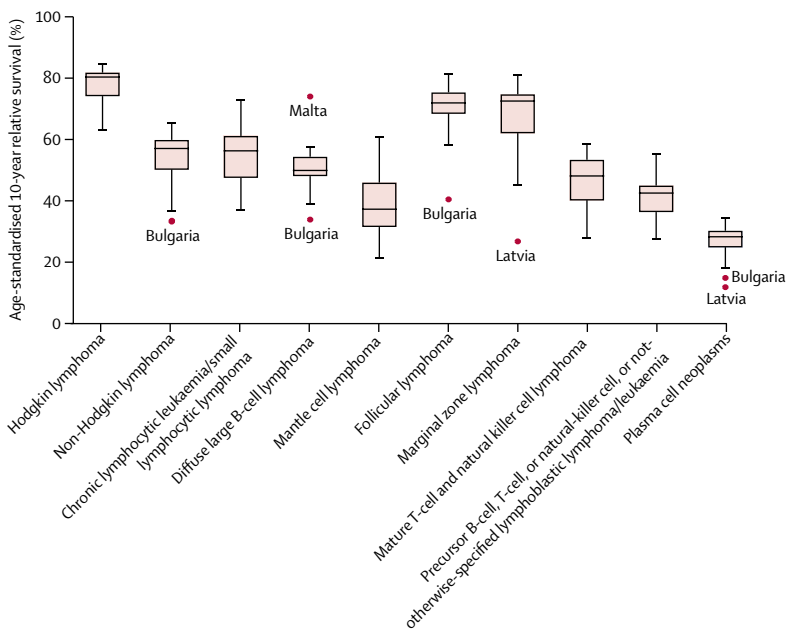


Figure 2: **10-year relative survival for adult patients followed up in 2010–14 in Europe, by age group for each lymphoid malignancy**
Data are presented as percentages with 95% CIs in parentheses.

in countries in the lowest quartile (low expenditure), with a graduated decrease in survival through the expenditure quartiles, although this pattern varied by lymphoid malignancy subgroup. The extent of these differences was similar for 5-year and 10-year ASRS.

Survival was similar and decreased only slightly from the first to the fourth total national health expenditure quartile for Hodgkin lymphoma, showing 10-year relative survival values of 82·7% (95% CI 81·6–83·8) in the first, 80·7% (79·8–81·6) in the second, 76·1%



Lymphoid malignancy*	I^2 statistic
Non-Hodgkin lymphoma	98·2%
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	97·6%
Plasma cell neoplasms	93·8%
Marginal zone lymphoma	92·7%
Hodgkin lymphoma	89·3%
Diffuse large B-cell lymphoma	87·0%
Follicular lymphoma	86·7%
Mantle cell lymphoma	86·1%
Mature T-cell and natural killer cell lymphoma	84·4%
Precursor B-cell, T-cell, or natural-killer cell, or not-otherwise-specified lymphoblastic lymphoma/leukaemia	73·5%

Figure 3: **Across-country variation in 10-year age-standardised relative survival, by each lymphoid malignancy**
Outliers fell outside the whiskers' length, defined as 1·5-times the IQR. *Descending order by I^2 statistics value.

(74·5–77·6) in the third, and 74·9% (73·3–76·3) in the fourth quartiles. The pattern was similar for non-Hodgkin lymphoma, but the gap between the first three quartiles and the fourth was much bigger: 59·3% (58·7–60·0) in the first, 57·6% (55·2–58·7) in the second, 55·4% (54·3–56·5) in the third, and 44·7% (43·6–45·8) in the fourth (appendix p 17).

The decrease through quartiles was less uniform for lymphoid malignancies with a poor prognosis: 10-year ASRS for mantle cell lymphoma ranged from 45·0% (95% CI 41·1–47·9) in the first quartile, to 31·3% (28·9–33·8) in the second, 36·6% (31·5–41·7) in the third, and 29·8% (22·3–37·1) in the fourth quartiles. The survival pattern for mature T and natural killer cell lymphoma ranged from 48·7% (95% CI 46·5–50·9) in the first to 45·3% (43·3–47·3) in the second, 46·0% (42·5–49·4) in the third, and 40·9% (36·3–45·3) in the fourth. The corresponding figures for plasma cell neoplasms were 29·8% (95% CI 28·8–30·8), 29·3% (28·5–30·1), 27·6% (26·2–28·9), and 22·5% (21·2–23·8).

In most countries in the first (high) or second (middle-high) total national health expenditure quartiles, 10-year ASRS was in line with or above the European mean for common lymphoid malignancies, such as Hodgkin lymphoma, non-Hodgkin lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma (figure 4; appendix pp 8–12).

Among countries in the third (middle-low) total national health expenditure group, 10-year ASRS was on average slightly below or close to the European average for Hodgkin lymphoma and non-Hodgkin lymphoma, respectively (figure 4; appendix pp 8–12).

In most countries in the fourth total national health expenditure quartile, ASRS values were lower than the European mean for many lymphoid malignancies (figure 4; appendix pp 8-12).

The multivariable regression models for each lymphoid malignancy 10-year RER adjusted by age, gender, and total national health expenditure quartiles found that RER increased with age at diagnosis for all lymphoid malignancies (table 3). Multivariable analysis confirmed higher survival for women than for men for all lymphoid malignancies, except precursor B, T, or natural killer cell, or not-otherwise-specified lymphoblastic lymphoma or leukaemia and hairy cell leukaemia.

With reference to the European mean, 10-year RER of all lymphoid malignancies increased with decreasing quartiles of TNHE, and countries in the highest TNHE quartile had lower RER than the European mean. For non-Hodgkin lymphoma, the RER ranged from 0·80 (95% CI 0·79–0·82), to 0·91 (0·90–0·93), 0·94 (0·92–0·96), and 1·45 (1·42–1·48) from the highest to the lowest total national health expenditure quartile.

The generalised linear models re-computed by two-way and three-way interaction effects did not show relevant differences in RERs with respect to the ones that considered only the main effects (appendix pp 21–22). In addition, the analyses performed in the subgroups defined for Hodgkin lymphoma and non-Hodgkin lymphoma did not account for remarkable differences in RERs (appendix p 23), thus showing that the effects of age, gender, and total national health expenditure seemed to be relevant only as main effects.

Discussion

Our population-based study of long-term survival for patients with lymphoid malignancies confirmed the previously reported geographical inequalities in short-to-medium-term survival.[7] The study also found that

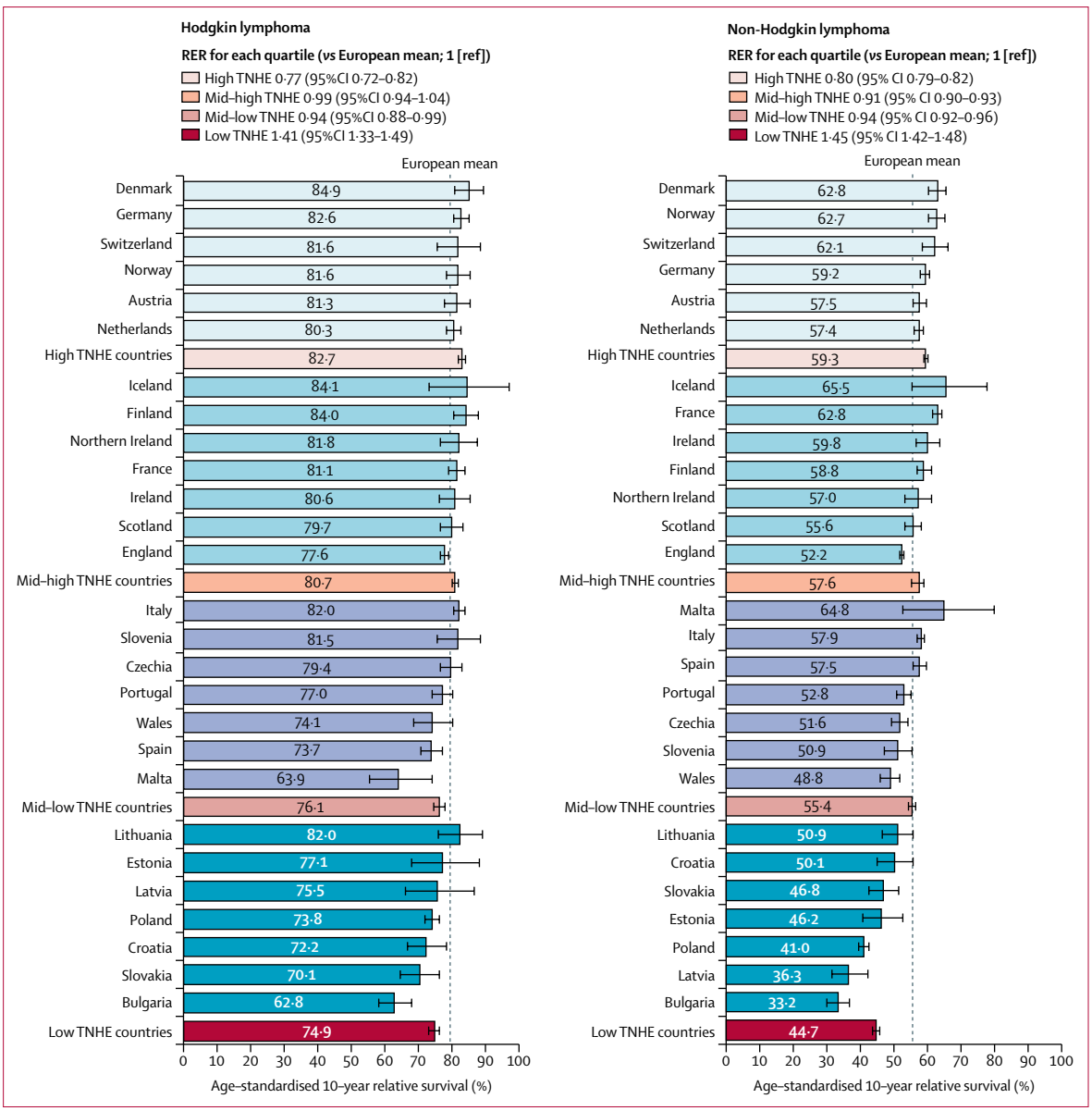


Figure 4: **10-year age-standardised relative survival for Hodgkin lymphoma and non-Hodgkin lymphoma in the EUROCARE-6 countries grouped by total national health expenditure quartile**

Data for age-standardised relative survival are presented as percentage, with 95% CI indicated by error bars. The data listed at the top of the figure are the RER estimates for each quartile, with reference to the European mean; the dotted line shows the European mean relative survival. RER=relative excess risk of death. TNHE=total national health expenditure. Graphs for all other lymphoid malignancies are provided in the appendix (pp 8–12).

long-term survival outcomes for patients with lymphoid malignancies are markedly associated with a country's overall investment in the health system (public or private), as measured by per-capita total national health expenditure. The categorisation of total national health expenditure into quartiles, rather than tertiles or quintiles, struck a balance between results granularity, statistical robustness and interpretability, making quartiles a preferred choice for grouping European countries based on their total national health expenditure (appendix pp 24–25). In countries with higher health-care expenditure, 10-year survival was better than in those with lower expenditures. This finding was true for all the lymphoid malignancies, although the survival decrease through the expenditure quartiles was not linear for all of them.

The survival advantage of women compared with men for most lymphoid malignancies, confirmed by multivariable analyses adjusted by age and total national health expenditure and consistent with other studies, might be due to earlier diagnosis, better health behaviours, or lower levels of multimorbidity.[30] Life

	Hodgkin Lymphoma	Non-Hodgkin Lymphoma	Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	Lymphoplasmacytic lymphoma/ Waldenström macroglobulinaemia	Diffuse large B-cell lymphoma	Mantle cell lymphoma	Follicular lymphoma	Marginal zone lymphoma	Mature T and natural killer cell lymphoma	Precursor B-cell, T-cell, natural killer, or not-otherwise-specified lymphoblastic lymphoma/ leukaemia	Plasma cell neoplasms	Hairy cell leukaemia
Age groups*												
15–54 years	NA	NA	NA	NA	NA	1 (ref)	NA	1 (ref)	NA	NA	NA	NA
15–44 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	NA	1 (ref)	NA	1 (ref)	1 (ref)	1 (ref)	1 (ref)
45–54 years	2·11 (1·87–2·37)	1·42 (1·35–1·49)	1·25 (1·09–1·45)	1·47 (0·89–2·42)	1·64 (1·51–1·79)	NA	1·49 (1·26–1·76)	NA	1·45 (1·27–1·64)	1·96 (1·75–2·19)	1·44 (1·31–1·58)	0·84 (0·38–1·88)
55–64 years	4·20 (3·80–4·64)	2·00 (1·91–2·09)	1·66 (1·45–1·90)	2·03 (1·27–3·24)	2·18 (2·02–2·35)	1·68 (1·43–1·98)	2·46 (2·11–2·86)	2·08 (1·72–2·52)	1·97 (1·76–2·21)	2·71 (2·46–2·99)	1·88 (1·73–2·05)	1·46 (0·69–3·10)
65–74 years	NA	2·92 (2·80–3·05)	2·45 (2·15–2·80)	3·12 (1·97–4·95)	3·11 (2·90–3·35)	2·59 (2·23–3·01)	3·45 (2·97–4·02)	3·18 (2·66–3·81)	2·52 (2·26–2·81)	NA	2·80 (2·58–3·05)	2·17 (1·01–4·68)
≥65 years	11·17 (10·33–12·08)	NA	NA	NA	NA	NA	NA	NA	NA	4·08 (3·76–4·43)	NA	NA
≥75 years	NA	5·54 (5·31–5·78)	4·39 (3·85–5·02)	6·14 (3·88–9·69)	5·64 (5·26–6·05)	4·56 (3·92–5·30)	7·46 (6·40–8·69)	5·66 (4·74–6·78)	3·96 (3·55–4·41)	NA	4·61 (4·24–5·02)	9·31 (4·64–18·68)
Gender												
Men	1·26 (1·18–1·49)	1·16 (1·14–1·19)	1·30 (1·26–1·35)	1·25 (1·13–1·39)	1·09 (1·06–1·12)	1·15 (1·06–1·24)	1·23 (1·15–1·32)	1·31 (1·18–1·46)	1·12 (1·05–1·19)	1·01 (0·94–1·08)	1·02 (1·00–1·05)	1·06 (0·70–1·60)
Women	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Total national health expenditure quartiles with countries†												
Low expenditure	1·41 (1·33–1·49)	1·45 (1·42–1·48)	1·66 (1·61–1·71)	1·62 (1·40–1·86)	1·22 (1·17–1·28)	1·26 (1·10–1·43)	1·69 (1·57–1·82)	2·49 (2·27–2·74)	1·26 (1·18–1·35)	1·18 (1·12–1·26)	1·28 (1·25–1·31)	2·15 (1·57–2·93)
Middle-low expenditure	0·94 (0·88–0·99)	0·94 (0·92–0·96)	1·04 (1·01–1·08)	1·09 (0·99–1·20)	0·97 (0·94–1·00)	0·86 (0·79–0·93)	0·85 (0·79–0·90)	0·82 (0·75–0·90)	0·83 (0·78–0·87)	1·05 (0·99–1·11)	0·94 (0·92–0·96)	1·13 (0·80–1·57)
Middle-high expenditure	0·99 (0·94–1·04)	0·91 (0·90–0·93)	0·83 (0·80–0·85)	0·90 (0·83–0·97)	0·96 (0·94–0·99)	1·14 (1·07–1·21)	0·85 (0·81–0·90)	0·70 (0·64–0·76)	1·01 (0·96–1·06)	0·89 (0·84–0·94)	0·94 (0·92–0·95)	0·76 (0·57–1·02)
High expenditure	0·77 (0·72–0·82)	0·80 (0·79–0·82)	0·70 (0·68–0·72)	0·63 (0·57–0·70)	0·88 (0·85–0·90)	0·82 (0·76–0·88)	0·82 (0·77–0·87)	0·70 (0·63–0·77)	0·95 (0·91–1·00)	0·90 (0·85–0·95)	0·89 (0·87–0·90)	0·54 (0·37–0·81)
European mean *vs* total national health expenditure quartiles	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Data are relative excess risk of death with 95% CI. Distinct models referring to each lymphoid malignancy were adjusted for age, sex, and total national health expenditure. Low-expenditure countries comprise Bulgaria, Croatia, Estonia, Latvia, Lithuania, Poland, and Slovakia; middle-low-expenditure countries comprise Czechia, Italy, Malta, Portugal, Slovenia, Spain, and Wales (UK); middle-high-expenditure countries comprise Finland, France, Iceland, Ireland, England (UK), Northern Ireland (UK), and Scotland (UK); high-expenditure countries comprise Austria, Denmark, Germany, the Netherlands, Norway, and Switzerland. NA=not available. Ref=reference group. *Groups for age at diagnosis were: 15–44, 45–54, 55–64, 65–74, and ≥75 years for non-Hodgkin lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia, diffuse large B-cell lymphoma, follicular lymphoma, mature T and natural killer cell lymphoma, plasma cell neoplasms, and hairy cell leukaemia; 15–54, 55–64, 65–74, and ≥75 years for mantle cell lymphoma and marginal zone lymphoma; and 15–44, 45–54, 55–64, and ≥65 years for Hodgkin lymphoma and precursor B-cell, T-cell, natural killer cell, or not-otherwise-specified lymphoblastic lymphoma/leukaemia. †Total national health expenditure in US$ purchasing power parity per capita.

***Table 3*: 10-year relative excess risk of death by age, sex, and total national health expenditure quartile, for each lymphoid malignancy**

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expectancy is better for women than for men everywhere, despite inequality in employment, income, and access to health care, and their increased survival might also be explained by genetic characteristics and immune responses mediated by sex hormones.

The steep relative survival decrease with age, evident for all lymphoid malignancies, indicates that poorer prognostic factors are concentrated in older patients. Older patients are more likely than younger ones to be undertreated because of comorbidity, medical contra-indications to full-dose chemotherapy,[11] chemotherapy-related toxicity,[16] and increased risk of undesired effects of anticancer treatments. Social isolation, poverty, and comorbidity are also more frequent among older people and are also associated with delayed cancer diagnoses and poorer outcomes.

The resources that a country can allocate for health care depend on its wealth, and total national health expenditure is directly related to gross national product.[9] Although the prices of oncological drugs vary across Europe and are lower in some regions than others, countries with lower incomes have more difficulty in allocating resources for expensive diagnostic equipment and treatment modalities, and find it harder to train and employ health personnel in all health sectors, than countries with higher incomes.

The high survival rates for people with Hodgkin lymphoma in countries with high and medium-high national health expenditure indicate that long-standing effective treatments have been deployed well in these countries, whereas the lower survival rates in lower health expenditure countries might be related to a paucity of health-care resources and poor organisation of care.

Clinical trials showed that diffuse large B-cell lymphoma is a potentially curable disease with an overall 60–70% chance of cure with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).[31] 10-year overall survival for patients with diffuse large B-cell lymphoma was 27·6% (95% CI 21·4–34·3) with CHOP only and 43·5% (36·4–50·4) with R-CHOP.[32] Other studies showed that overall survival for patients with follicular lymphoma improved significantly since the introduction of rituximab. The Swedish Lymphoma Registry reported 10-year overall survival for patients with follicular lymphoma from 2003 to 2010 to be 92% for those aged 18–49 years, 83% for those aged 50–59 years, 78% for those aged 60–69 years, and 64% for those aged 70 years or older,[33] and US and French cohorts' results confirmed improved overall survival for patients with follicular lymphoma with rituximab (10-year overall survival of approximately 80%), compared with without rituximab.[34]

We suppose that the small differences in survival for patients with diffuse large B-cell lymphoma (and the whole non-Hodgkin lymphoma group) across the second and third total national health expenditure quartiles and among countries of the same quartile might be related to the availability of effective drugs, such as rituximab, and protocols, such as R-CHOP.[35] These new options for patients with non-Hodgkin lymphoma have been in clinical use since 2000 and have coincided with many lymphoid malignancy survival gains, especially for patients with follicular lymphoma and diffuse large B-cell lymphoma, as we observed. Unfortunately, we do not have detailed information about each country's adoption of protocols. Notably, new regimens are more expensive than previous ones, for single-agent cost (ie, rituximab or immunotherapy) and for the complexity of treatment schemes.

When prognosis was uniformly poor, as for patients with plasma cell neoplasms or mantle cell lymphoma, there was little difference in 10-year survival and RER through the TNHE quartiles, with differences mainly occurring between the highest and lowest quartiles. RER and survival differences across total national health expenditure quartiles were more important when diagnostic modalities and accuracy differed widely between countries. Chronic lymphocytic leukaemia/small lymphocytic lymphoma is a major diagnostic challenge: the concept of pre-malignant clonal proliferation has been introduced for its classification, with a blood clonal population cutoff of 5000 B lymphocytes per mm^3.[36] Distinction between mantle cell lymphoma, chronic lymphocytic leukaemia, atypical chronic lymphocytic leukaemia, and some marginal zone lymphomas was not straightforward as the differential diagnosis required immunophenotype, and cytogenetic and molecular analyses. Revision of cancer registry procedures to include specific surveillance should help ensure more accurate chronic lymphocytic leukaemia/small lymphocytic lymphoma monitoring. Possible under-registration of lymphoplasmacytic lymphoma/Waldenström macro-globulinaemia and chronic lymphocytic leukaemia/small lymphocytic lymphoma might be due to patients being diagnosed and treated in outpatient clinics, with only more advanced cases or late diagnoses recorded in cancer registry databases.

We found a positive association between total national health expenditure and lymphoid malignancy 10-year survival but not in all countries. The UK—at middle-high national health expenditure quartile—showed lower survival than the European mean for six of the 12 lymphoid malignancies analysed, and Finland had lower survival than the European mean for chronic lymphocytic leukaemia/small lymphocytic lymphoma. In countries with high total national health expenditure, lower survival might be due to inefficient health systems delivering poorer value-for-money care. By contrast, the high survival in Italy for Hodgkin lymphoma and non-Hodgkin lymphoma might indicate good health-care value-for-money and efficient use of scarce resources.

Our study has some limitations. First, this is an observational, retrospective, population-based study with the main goal of providing an understanding of the

state of affairs in lymphoid malignancy survival in Europe and to represent a benchmark for future analyses. The relationship between total national health expenditure and lymphoid malignancy survival could be influenced by various factors, such as diagnostic capacity, treatment accessibility, quality of care, surveillance, and health-care professional expertise. Unfortunately, the only available confounders in this study are age at diagnosis, gender, and period of diagnosis. Including a broader range of confounders would have enhanced the validity of our findings.

Second, this study is based on incidence data referring to 10 years ago on average, but they are the most recent data available.[14] Several factors contributed to delays in such a comprehensive study conduction that, notably, ensures maximum geographical representativeness, an essential strength of this study. The lag in cancer registry data recording in Europe, depending on country-specific operational conditions (scarce dedicated resources available, organisation of electronic health-care data, digitisation of processes, and compliance with local privacy regulations) resulted in different data collection times. Moreover, quality controls, which involved multiple revisions and submissions, to ensure maximum result comparability and high data quality, required additional time to permit all data analyses. Plans for the new EUROCARE round include recruitment of patients diagnosed up to 2021 and followed up to the end of 2022. A more flexible strategy to include updates of registry data is envisaged to improve the timeliness of estimations. Furthermore, the process of error checks and correction will be further automated to speed up the analyses.

In addition, changes in the classification of lymphoid malignancies during the study period impaired the conversion of some old codes to newer ones, leading to fairly high proportions of not-otherwise-specified morphologies.

Finally, total national health expenditure might not depict regional cancer registry areas because it represents the whole country. In Italy, most cases were provided by cancer registries in the wealthier northern and central areas. The centralisation of care for haematological malignancies in specialised hospitals can also contribute to relatively good outcomes.[37]

In conclusion, survival inequalities in patients with lymphoid malignancies uncovered in the past are still evident in more recent years and persist in the long-term follow-up. In countries with low total national health expenditure, policy decisions are needed to increase health-care resources and identify strategies to sustain interventions. Differences in lymphoid malignancy survival among countries with similar total national health expenditure suggest the need for investigation of national health-care policies and health resource utilisation for lymphoid malignancies. In all countries, the implementation and dissemination of efficient, evidence-based models of care, including long-term surveillance, is needed to reduce inequalities. Given the high (and rising) cost of drugs for haematological malignancies, political pressure and negotiations with drug manufacturers to reduce prices of the most expensive drugs should be pursued.

Contributors

MS designed the study, drafted the study protocol, supervised the entire work, and drafted most of the initial version of the report. CV designed the study, drafted the study protocol, and contributed to define quality controls. SR, RL, and RDA did all statistical analyses and wrote the relevant parts of the report. SB prepared all tables and figures, and contributed to statistical analyses and quality controls. MS, CV, SR, SB, ED, and RDA prepared the data and did the quality controls. SR, RL, RDA, MS, CV, SB, and ED accessed and verified the data. MS, CV, RL, SR, SB, RM-G, MM, KI, KP, OV, ED, AB, CDB, SMM, MB, PW, DB, DS, and RDA contributed to interpreting the results. The EUROCARE-6 Working Group revised the study protocol, collected, prepared, and transmitted raw data to the study database, corrected data after quality controls, checked the results of the analyses, and revised the Article. All authors contributed to data interpretation and rewriting of the Article, and reviewed and approved the final version. All the participating cancer registries collected and prepared the data as part of their essential role in cancer control. MS, CV, SR, SB, RL, ED, RDA, AB, and CDB had full access to all the data and all authors had final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

We analysed pseudonymised data collected from 82 population-based cancer registries, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analyses agreed in the EUROCARE-6 protocol. We are not permitted to share individual-level data. Aggregated-level data, in the form of counts, rates, or survival proportions, can be only shared after express permission from the participating registries. These data should be requested by contacting the corresponding author or the Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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