Changes in dynamics of excess mortality rates and net survival after diagnosis of follicular lymphoma or diffuse large B-cell lymphoma: comparison between European population-based data (EUROCARE-5)

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Summary

Background Since 2001, the *World Health Organization classification of tumours of haematopoietic and lymphoid tissues* and the *International Classification of Diseases for Oncology (third edition)* have improved data collection for lymphoma subtypes in most European cancer registries and allowed reporting on the major non-Hodgkin lymphoma subtypes. Treatment of non-Hodgkin lymphoma has changed profoundly, benefiting patients with follicular lymphoma or diffuse large B-cell lymphoma. We aimed to compare dynamics of cancer mortality in patients with follicular lymphoma or diffuse large B-cell lymphoma in five large European areas using data for survival from the largest number of collaborative European population-based cancer registries (EUROCARE).

Methods We considered follicular lymphoma and diffuse large B-cell lymphoma cases in patients aged older than 15 years diagnosed between Jan 1, 1996, and Dec 31, 2004, and recorded in 43 cancer registries in five areas: Scotland and Wales, and northern, central, eastern, and southern Europe. We excluded cases incidentally diagnosed at autopsy or known from death certificates only. The vital status could be updated on Dec 31, 2008, in all registries but the French ones (Dec 31, 2007). We obtained changes in net survival with the Pohar-Perme estimator and excess mortality rate with a flexible parametric model according to age and year of diagnosis.

Findings We identified 13 988 follicular lymphoma and 25 320 diffuse large B-cell lymphoma cases. We noted improvements in 5-year net survival for all ages between the 1999–2001 and 2002–04 periods for both cancers (except for follicular lymphoma in Scotland and Wales and diffuse large B-cell lymphoma in eastern Europe). For follicular lymphoma, 5-year net survival in northern Europe was 64% (95% CI 58–71) in 1999–2001 versus 75% (69–80) for 2002–04, for Scotland and Wales, it was 71% (66–76) versus 68% (64–72), for central Europe, it was 64% (61–67) versus 72% (70–75), for southern Europe, it was 67% (63–70) versus 73% (70–76), and for eastern Europe, it was 50% (43–57) versus 61% (54–69). For diffuse large B-cell lymphoma, 5-year net survival in northern Europe was 41% (35–49) versus 58% (54–62), in Scotland and Wales, it was 44% (41–48) versus 52% (49–54), in central Europe, it was 46% (44–47) versus 50% (48–51), in southern Europe, it was 44% (42–47) versus 50% (48–52), and in eastern Europe, it was 47% (41–54) versus 46% (43–50). We noted the largest area disparity during the 2002–04 period between eastern and northern Europe. We noted a significant effect of the year of diagnosis on the excess mortality rate for all ages in all areas, except for diffuse large B-cell lymphoma in eastern Europe. The excess mortality rate was not constant during the follow-up period: we noted a high rate early for both lymphomas, except for follicular lymphoma in northern Europe.

Interpretation Although survival for follicular lymphoma and diffuse large B-cell lymphoma is improving, the results from this study should foster the search for more and better means of improvement of access to adequate care than that at present, as there remains variation in survival between European regions. Study of the dynamics of the excess mortality rate seems to be a useful clinical indicator to help the practitioner's choice of optimum management of patients.

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Introduction

Non-Hodgkin lymphoma is a large heterogeneous group of lymphoid neoplasms with distinct biological, clinical, and prognostic features. This heterogeneity emphasises the importance of epidemiological results being reported per subtype.[1] The 2001 *World Health Organization classification of tumours of haematopoietic and lymphoid tissues*[2] and the *International Classification of Diseases for Oncology (third edition*; ICD-O-3)[3] have improved data collection for lymphoma subtypes in most European cancer registries and allowed the major non-Hodgkin lymphoma subtypes to be reported on. For lymphoma, the new classification

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Research in context

Evidence before this study

European collaborations allowed the EUROCARE cancer database to be built. Simultaneously, the HAEMACARE project improved the availability and homogeneity of haematological cancer data in Europe. Both enabled more reliable comparisons between countries than were previously possible. We searched PubMed for articles published between Jan 1, 1995, and Feb 1, 2015, with no language restrictions, using the following search terms: "population-based registries", "follicular lymphoma", "diffuse large B cell lymphoma", "non Hodgkin lymphoma", "EUROCARE", "CONCORD", "treatment managment in NHL", "excess mortality", "comparison of survival trends". Findings from a previous EUROCARE-5 study showed improvements in survival after non-Hodgkin lymphoma in Europe on the basis of population-based data, especially follicular lymphoma and diffuse large B-cell lymphoma. With improved disease knowledge and use of new drugs in non-Hodgkin lymphoma therapeutic management, study of specific follicular lymphoma and diffuse large B-cell lymphoma excess mortality on the basis of population-based data seems important to compare differences between European areas in managment of these lymphomas since 1996.

Added value of this study

This study assesses the change in dynamics of the excess mortality rate (EMR) and net survival after follicular lymphoma or diffuse large B-cell lymphoma and compares survival between five large European areas. It reports comparison using the probability of net survival (the most appropriate indicator for comparisons between areas) and its associated EMR during 5 years of follow-up. Additionally, the study offers original flexible parametric modelling of the EMR in follicular lymphoma and diffuse large B-cell lymphoma, allowing the effects of age at and year of diagnosis to be linear or non-linear and proportional or non-proportional.

Implications of all the available evidence

Study of the dynamics of EMRs and the corresponding net survival values helps visualisation of variations during follow-up and between-area disparities. The results from this study should foster the search for more and better means of improvement of access to adequate care than at present.

was largely based on the *Revised European American Lymphoma Classification* published in 1994.

Meanwhile, two major advances occurred: improved disease knowledge and development of the anti-CD20 chimeric monoclonal antibody rituximab. Patients with follicular lymphoma or diffuse large B-cell lymphoma were the first to benefit from rituximab immunotherapy, which improved overall survival in many clinical trials[4,5] or population-based studies.[6] However, disparities in drug availability between European regions created survival differences between periods of diagnosis or ages at diagnosis.[6] The HAEMACARE project improved the coding rules of lymphoid neoplasms in Europe and published the first relative survival probabilities after major non-Hodgkin lymphoma subtypes between 2000 and 2002.[7] In an update,[8] changes in 5-year relative survival after major haematological malignancy subtypes between 1997–99 and 2006–08 showed persistent survival differences across Europe.

Interpretation of differences in all-cause survival after cancer between areas is difficult because differences in noted mortalities could be due to differences in expected and not cancer-specific mortalities. An alternative is to compare net survival—ie, the probabilities of survival if disease is the only cause of death.[9] Net survival is obtained from the excess mortality rate (EMR), which is estimated by removal of the expected mortality rate from other causes from the noted mortality rate of the patients with cancer. This expected mortality rate from other causes is deemed equal to the all-cause mortality in the general population, with the assumption that the disease-specific mortality is negligible versus other-cause mortality. The EMR estimates how much higher the mortality rate of patients with cancer is than that expected in the general population.

To obtain unbiased estimates of net survival, informative censoring needs to be allowed (ie, due to covariates with simultaneous effects on disease-specific and other-cause mortalities, such as age).[10,11] This censoring is ensured by two methods: the Pohar-Perme non-parametric estimator[12] and the additive excess mortality model,[13,14] adjusted for demographic covariates. Because the effects of some covariates (age or year of diagnosis) on the excess hazard of death can change over time elapsed since diagnosis, and because the effects of some continuous covariates might be non-linear, a flexible excess hazard model was developed[14] to model these effects simultaneously. This model allows the dynamics of the EMR to be explored during the follow-up period and the change in these dynamics to be investigated according to the year of diagnosis.

In this study, we use data for survival collected by the largest number of collaborative European population-based cancer registries (EUROCARE). We compare the dynamics of follicular lymphoma and diffuse large B-cell lymphoma EMR and net survival between European regions.

Methods

Study design and data collection

The present EUROCARE-5 project includes more than 21 million cancers recorded in 107 population-based registries from 30 European countries. The following are available for each patient: sex, date of birth, date of cancer

diagnosis, cancer morphology and topography, basis of diagnosis, vital status, and date of death or last known vital status.

We coded the neoplasm morphology according to the ICD-O-3.[3] A standardised quality control searched for inconsistencies, such as mismatches between sex, age, topography, and morphology. We checked dubious records with inconsistencies at the registries and confirmed or corrected them.[6] We deemed eligible all follicular lymphomas and diffuse large B-cell lymphomas diagnosed between Jan 1, 1996, and Dec 31, 2004, in people aged 15 years or older. As usual in EUROCARE and all cancer survival studies, we excluded cases incidentally diagnosed at autopsy or known from death certificates only. We followed the vital status until Dec 31, 2008, in all registries but the French ones (Dec 31, 2007).

We based the lymphoma groups on the WHO classification.[2] For follicular lymphoma, we considered ICD-O-3 codes 9675/3 (follicular lymphoma, used before 2000 but not thereafter for mixed small-cell and large-cell diffuse malignant lymphoma), 9690/3 (follicular lymphoma, not otherwise specified), and 9695/3 (follicular lymphoma grade 1), 9691/3 (follicular lymphoma grade 2), and 9698/3 (follicular lymphomas grade 3). For diffuse large B-cell lymphoma, we considered codes 9678/3 (primary effusion lymphoma), 9679/3 (mediastinal large B-cell lymphoma), 9680/3 (diffuse large B-cell lymphoma), and 9684/3 (immunoblastic large B-cell diffuse lymphoma).

After receiving written consent of the cancer registries to participate, we kept only those with complete incidence data registration (54 registries). Indicators of exhaustiveness were the percentages of unspecified cases and loss to follow-up. Consistent with previous EUROCARE studies, we excluded cancer registries that reported more than 30% lymphoid neoplasms as not otherwise specified of all non-Hodgkin lymphomas diagnosed between 1996 and 2004 (ie, ICD-O-3 codes 9590/3 for lymphoma not otherwise specified and 9591/3 for non-Hodgkin lymphoma not otherwise specified; 11 registries excluded).

The study included 43 population-based cancer registries grouped into five areas: northern Europe (Iceland and Norway), Scotland and Wales, central Europe (France, Germany, Switzerland, and the Netherlands), southern Europe (Italy, Malta, Slovenia, and Spain), and eastern Europe (Estonia, Lithuania, and Slovakia).

	Cases				Quality indicators (diffuse large B-cell and follicular lymphoma [loss to follow-up])	Excluded (diffuse large B-cell and follicular lymphoma [DCO or autopsy])	Included	
	All non-Hodgkin lymphomas	Diffuse large B-cell lymphoma	Follicular lymphoma	Unspecified			Diffuse large B-cell lymphoma	Follicular lymphoma
Northern Europe	8581	1468 (17%)	1235 (14%)	1863 (22%)	3 (<1%)	4 (<1%)	1465 (99·5%)	1234 (99·5%)
Iceland	451	129 (29%)	71 (16%)	17 (4%)	0	3 (2%)	126 (98%)	71 (100%)
Norway	8130	1339 (16%)	1164 (14%)	1846 (23%)	3 (<1%)	1 (<1%)	1339 (100%)	1163 (99·5%)
Scotland and Wales	16 491	2972 (18%)	1985 (12%)	4408 (27%)	1 (<1%)	10 (<1%)	2964 (99·5%)	1983 (99·5%)
Scotland	10 338	2012 (19%)	1327 (13%)	2564 (25%)	1 (<1%)	8 (<1%)	2006 (99·5%)	1325 (99·5%)
Wales	6153	960 (16%)	658 (11%)	1844 (29%)	0	2 (<1%)	958 (99·5%)	658 (100%)
Central Europe	44 550	11 923 (27%)	6507 (15%)	4452 (10%)	227 (1%)	93 (1%)	11 840* (99%)	6495 (99·5%)*
France								
Bas-Rhin	1763	410 (23%)	186 (11%)	226 (13%)	16 (3%)	0	410 (100%)	186 (100%)
Côte-d'Or	1135	258 (23%)	141 (12%)	85 (7%)	3 (1%)	0	258 (100%)	141 (100%)
Doubs	959	218 (23%)	128 (13%)	35 (4%)	3 (1%)	0	218 (100%)	128 (100%)
Hérault	1720	463 (27%)	265 (15%)	78 (5%)	39 (5%)	0	463 (100%)	265 (100%)
Isère	1999	525 (26%)	271 (14%)	141 (7%)	17 (2%)	0	525 (100%)	271 (100%)
Somme	942	277 (29%)	106 (11%)	69 (7%)	5 (1%)	0	277 (100%)	106 (100%)
Tarn	708	206 (29%)	107 (15%)	32 (5%)	4 (1%)	0	206 (100%)	107 (100%)
Germany								
Hambourg	3438	516 (15%)	452 (13%)	890 (26%)	26 (3%)	3 (<1%)	513 (99%)	452 (100%)
Saarland	2125	493 (23%)	314 (15%)	369 (17%)	0	1 (<1%)	492 (99·5%)	314 (100%)
Switzerland								
Basel	825	275 (33%)	101 (12%)	69 (8%)	40 (11%)	14 (4%)	262 (95%)	100 (99%)
Grisons	403	102 (25%)	44 (11%)	68 (17%)	1 (1%)	0	102 (100%)	44 (100%)
St Gallen	920	242 (26%)	134 (15%)	84 (9%)	2 (1%)	3 (1%)	239 (99%)	134 (100%)

(Table continues on next page)

	Cases				Quality indicators (diffuse large B-cell and follicular lymphoma [loss to follow-up])	Excluded (diffuse large B-cell and follicular lymphoma [DCO or autopsy])	Included	
	All non-Hodgkin lymphomas	Diffuse large B-cell lymphoma	Follicular lymphoma	Unspecified			Diffuse large B-cell lymphoma	Follicular lymphoma
(Continued from previous page)								
Valais	492	112 (23%)	61 (12%)	47 (10%)	3 (2%)	0	112 (100%)	61 (100%)
Netherlands	27121	7826 (29%)	4197 (15%)	2259 (8%)	68 (1%)	72 (1%)	7763 (99%)*	4186 (99·5%)*
Southern Europe	31123	7340 (24%)	3483 (11%)	4718 (15%)	205 (2%)	50 (1%)	7296 (99%)	3477 (99·5%)
Italy								
Alto Adige	975	234 (24%)	92 (9%)	45 (5%)	0	0	234 (100%)	92 (100%)
Biella	556	128 (23%)	90 (16%)	31 (6%)	0	0	128 (100%)	90 (100%)
Ferrara	1097	278 (25%)	90 (8%)	132 (12%)	4 (1%)	6 (2%)	272 (98%)	90 (100%)
Genova	2748	654 (24%)	404 (15%)	265 (10%)	0	1 (<1%)	653 (99·5%)	404 (100%)
Latina	721	185 (26%)	78 (11%)	200 (28%)	10 (4%)	0	185 (100%)	78 (100%)
Modena	1848	488 (26%)	188 (10%)	66 (4%)	9 (1%)	0	488 (100%)	188 (100%)
Napoli	750	172 (23%)	114 (15%)	208 (28%)	6 (2%)	0	172 (100%)	114 (100%)
Parma	1235	339 (27%)	91 (7%)	344 (28%)	12 (3%)	0	339 (100%)	91 (100%)
Ragusa	467	86 (18%)	53 (11%)	89 (19%)	0	0	86 (100%)	53 (100%)
Reggio Emilia	1261	269 (21%)	105 (8%)	321 (25%)	3 (1%)	0	269 (100%)	105 (100%)
Romagna	3042	772 (25%)	243 (8%)	408 (13%)	0	1 (<1%)	772 (100%)	242 (99·5%)
Sassari	934	243 (26%)	117 (13%)	106 (11%)	0	0	243 (100%)	117 (100%)
Trentino	974	176 (18%)	131 (13%)	264 (27%)	0	0	176 (100%)	131 (100%)
Varese	2148	432 (20%)	245 (11%)	466 (22%)	13 (2%)	2 (<1%)	432 (100%)	243 (99%)
Malta	535	93 (17%)	71 (13%)	134 (25%)	1 (1%)	0	93 (100%)	71 (100%)
Slovenia	2810	660 (23%)	177 (6%)	450 (16%)	0	19 (2%)	641 (97%)	177 (100%)
Spain								
Basque Country	3471	854 (25%)	522 (15%)	554 (16%)	40 (3%)	12 (1%)	844 (99%)	520 (99·5%)
Girona	1080	270 (25%)	155 (14%)	68 (6%)	10 (2%)	1 (<1%)	269 (99·5%)	155 (100%)
Granada	992	257 (26%)	127 (13%)	75 (8%)	3 (1%)	0	257 (100%)	127 (100%)
Murcia	1399	253 (18%)	183 (13%)	216 (15%)	94 (22%)	1 (<1%)	252 (99·5%)	183 (100%)
Navarra	966	249 (26%)	99 (10%)	117 (12%)	0	3 (1%)	246 (99%)	99 (100%)
Tarragona	1114	248 (22%)	108 (10%)	159 (14%)	0	4 (1%)	245 (99%)	107 (99%)
Eastern Europe	11072	1782 (16%)	823 (7%)	2096 (19%)	20 (1%)	51 (2%)	1755 (98%)	799 (97%)
Estonia	1772	303 (17%)	185 (10%)	251 (14%)	0	2 (<1%)	302 (99·5%)	184 (99%)
Lithuania	3775	469 (12%)	103 (3%)	896 (24%)	20 (4%)	5 (1%)	465 (99%)	102 (99%)
Slovakia	5525	1010 (18%)	535 (10%)	949 (17%)	0	44 (3%)	988 (98%)	513 (96%)
EUROCARE pool	111817	25485 (23%)	14033 (13%)	17537 (16%)	456 (1%)	208 (1%)	25320 (99%)*	13988 (99·5%)*

Data are n or n (%). DCO=death certificate only. *One additional patient excluded because their sex was unspecified.

Table: **Indicators of data quality in the cancer registries**

Estimation of net survival

We estimated net survival probabilities (with 95% CIs) with the Pohar-Perme estimator.[12] We estimated 5-year net survival per subtype, area, age at diagnosis (15–44 years, 45–64 years, 65–74 years, and 75 years and older), period of diagnosis (1996–98, 1999–2001, and 2002–04), and sex. We obtained general population life-tables from registry-specific official mortality data stratified by sex, age (in 1-year groups), and calendar year. We age standardised net survival estimates according to the International Cancer Survival Standards.[15] These survival analyses used the package relsurv (version 1.6.4).

Statistical modelling of the EMR

We used a flexible version of the excess mortality models[14] to quantify the effects of the year of diagnosis on mortality. This approach uses regression splines and allows for non-proportional (ie, time dependent) and non-linear covariate effects. For each area and subtype, we modelled the EMR up to 5 years after diagnosis, modelling the baseline hazard as a continuous function.

The covariates considered were age at and year of diagnosis. The effect of age is known to be non-linear and time dependent,[16] therefore we systematically specified both characteristics in the considered models. For the year

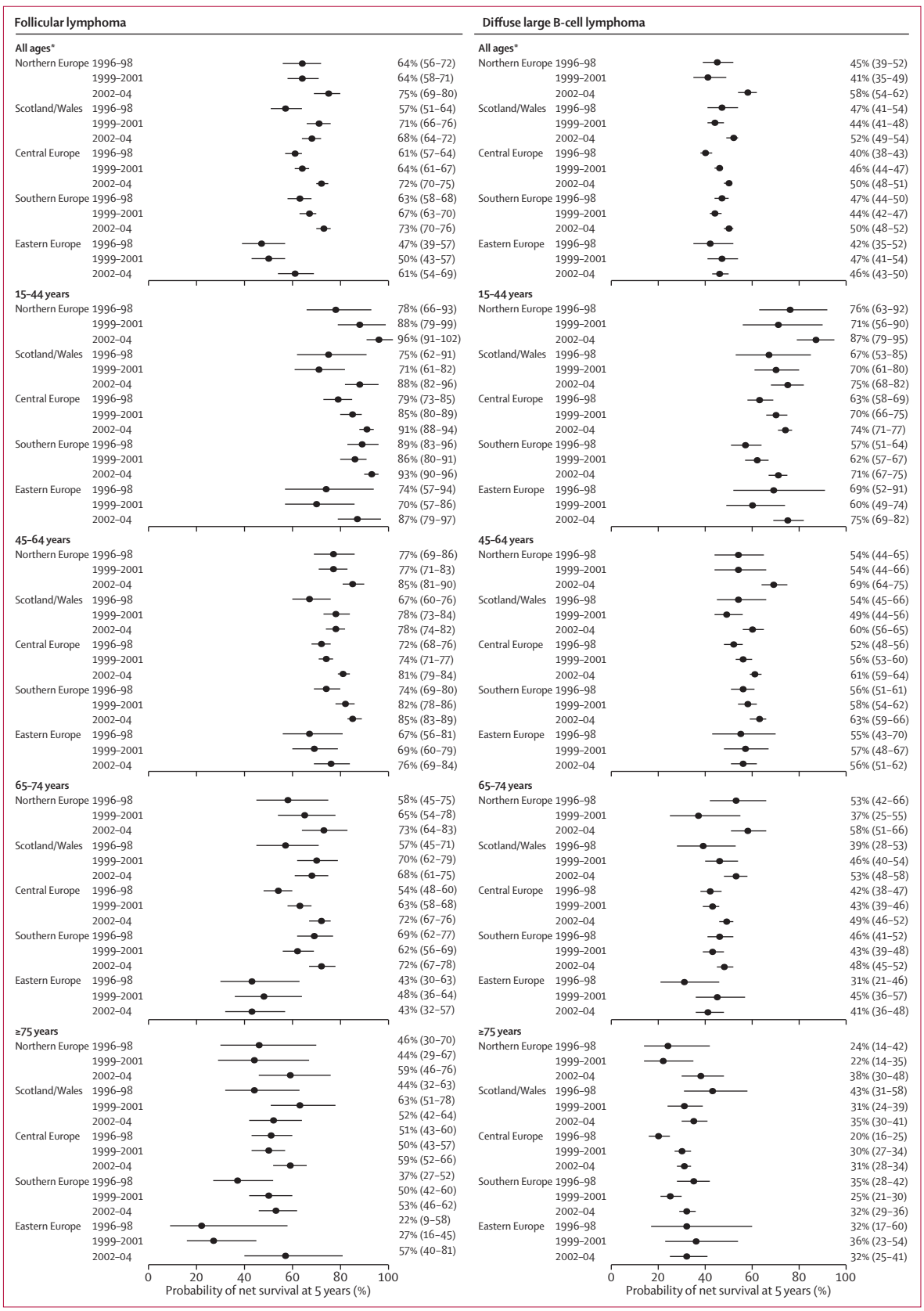

Figure 1: **Age-standardised net survival and age-class net survival at 5 years after follicular lymphoma or diffuse large B-cell lymphoma**
Data in parentheses are 95% CIs. *Age-standardised net survival with use of the International Cancer Survival Standards.[15]

of diagnosis, we selected the effects to include (non-linear or time dependent) with a specific model-building strategy[17] applied separately for each area and subtype (appendix pp 7, 8). We obtained EMR dynamics and trends of 5-year net survival at specific ages and years of diagnosis from the final model; the curves (for EMR or net survival) are then continuous and possibly non-linear according to the retained model. For EMR modelling, we used functions previously developed in R software.[14]

See Online for appendix

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MMo had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

We analysed 13 988 follicular lymphoma and 25 320 diffuse large B-cell lymphoma cases, whose characteristics are shown in the appendix (pp 2, 3). The data quality control results are shown in the table. Loss to follow-up in the five European areas was 2% or less (several individual countries had a more than 2% loss to follow-up). We excluded only 0·5% (208 of 39 518 cases) of all follicular lymphoma and diffuse large B-cell lymphoma cases from the analyses

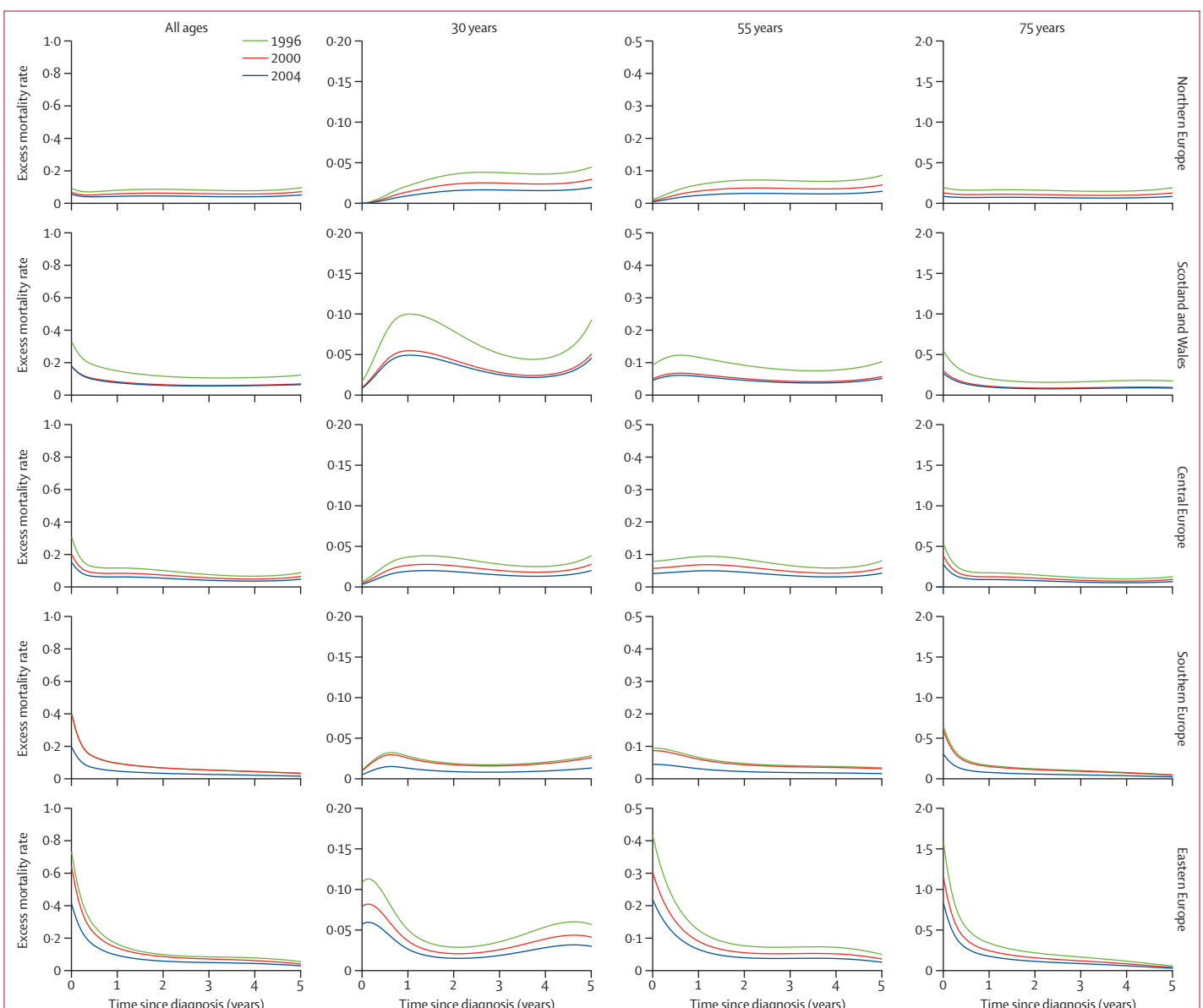

Figure 2: **Dynamics of the excess mortality rates in follicular lymphoma**
Results of the finally retained model for each European area. Please note that different y axis scales are used.

because they were diagnosed at autopsy (159 [0·4%]) or registered from death certificates (49 [0·1%]).

Women constituted more of the follicular lymphoma cases than did men: 7408 (53%) of all 13 988 cases, but 462 (58%) of 799 eastern European cases (appendix p 2). Follicular lymphoma affected all age categories. The median age at diagnosis was 62 years (IQR 51–72; 1815 [13%] of those aged 15–44 years, 6144 [44%] aged 45–64 years, 3342 [24%] aged 65–74 years, and 2687 [19%] aged 75 years and older). In the whole cohort, 4882 (35%) patients with follicular lymphoma died within 5 years of diagnosis: 389 (32%) of 1234 in northern Europe, 1111 (32%) of 3477 in southern Europe, 2271 (35%) of 6495 in central Europe, 358 (45%) of 799 in eastern Europe, and 753 (38%) of 1983 in Scotland and Wales. Median follow-up for all areas was 8 years (IQR 6–10).

Men constituted more of the diffuse large B-cell lymphoma cases than did women: 13 081 (52%) of all 25 320 cases, with the lowest proportion in eastern Europe (802 [46%] of 1755) and the highest proportion in northern (782 [53%] of 1465) and central (6247 [53%] of 11 840) European cases (appendix p 3). Diffuse large B-cell lymphoma predominantly occurred in older individuals. Median age at diagnosis was 68 years

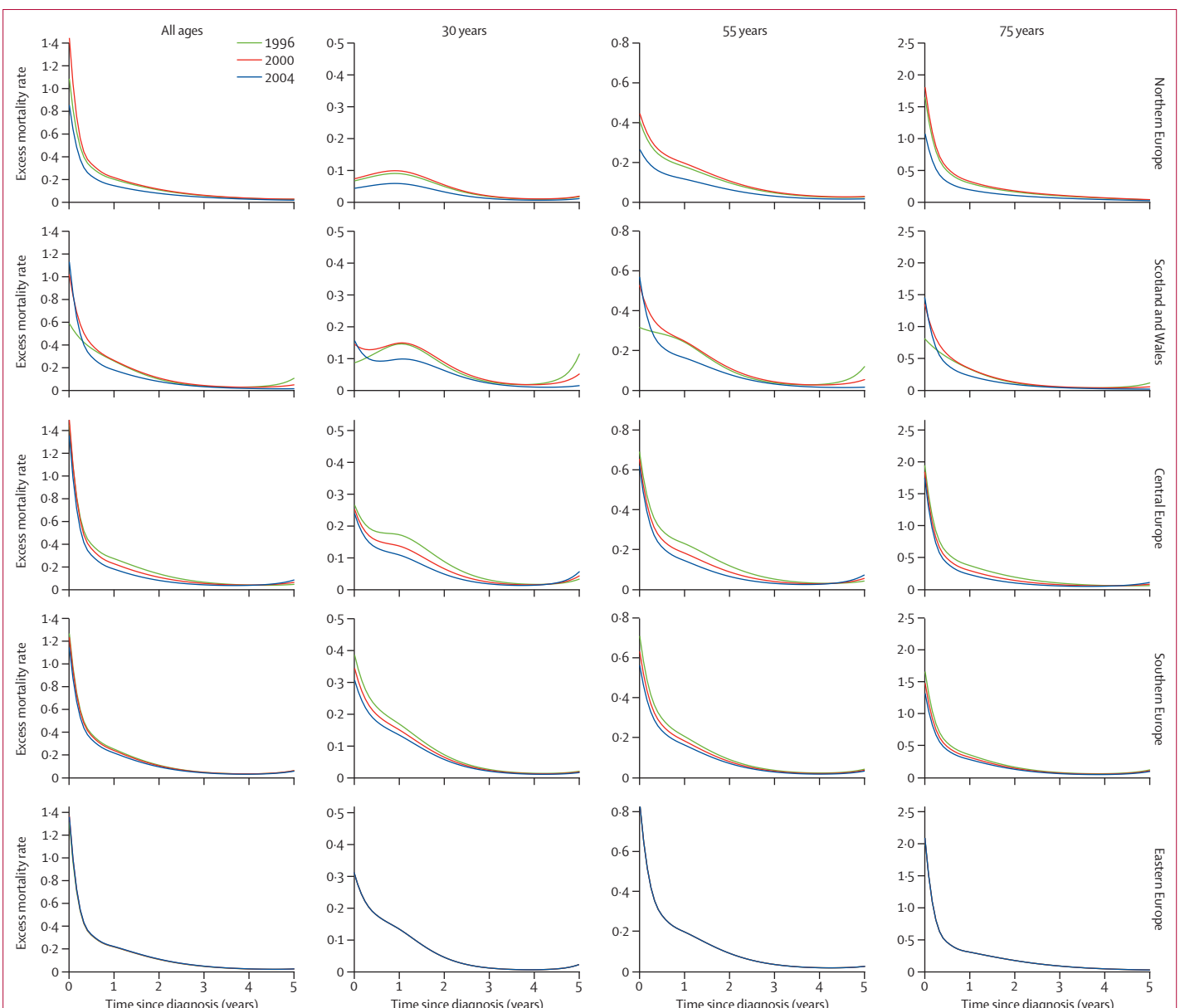

Figure 3: **Dynamics of the excess mortality rates in diffuse large B-cell lymphoma**
Results of the finally retained model for each European area. Please note that different y axis scales are used.

(IQR 55–75; 3328 [13%] of those aged 15–44 years, 7261 [29%] aged 45–64 years, 6669 [26%] aged 65–74 years, and 8062 [32%] aged 75 years and older). In the whole cohort, 14484 (57%) patients with diffuse large B-cell lymphoma died within 5 years of diagnosis: 790 (54%) of 1465 in northern Europe, 4140 (57%) of 7296 in southern Europe, 6843 (58%) of 11840 in central Europe, 1006 (57%) of 1755 in eastern Europe, and 1705 (58%) of 2964 in Scotland and Wales. Median follow-up for all areas was 7 years (IQR 5–10).

We estimated age-specific and age-standardised net survival probabilities at 5 years over 3-year periods of diagnosis for each area and subtype (figure 1). The number at risk in each group and the number of deaths at 5 years are shown in the appendix (pp 4, 5). Net survival increased between the 1999–2001 and 2002–04 periods in all regions for both cancers, except for follicular lymphoma in Scotland and Wales and diffuse large B-cell lymphoma in eastern Europe, where they remained stable after 2001. Whatever the age class, the largest net survival disparity occurred between eastern and northern Europe during the 2002–04 period: the 5-year age-standardised net survival was 61% (95% CI 54–69) in eastern Europe versus 75% (69–80) in northern Europe for follicular lymphoma and 46% (43–50) versus 58% (54–62) for diffuse large B-cell lymphoma. Irrespective of subtype, net survival was the lowest in the oldest patients. The largest difference in 5-year net survival according to age in the 2002–04 period occurred in southern Europe for follicular lymphoma (93% [90–96] for patients aged 15–44 years *vs* 53% [46–62] for those aged 75 years and more) and northern Europe for diffuse large B-cell lymphoma (87% [79–95] for patients aged 15–44 years versus 38% [30–48] for those aged 75 years and more). The 5-year net survival in follicular lymphoma was slightly higher in women than in men in both European areas; this difference was less marked in diffuse large B-cell lymphoma (appendix p 6).

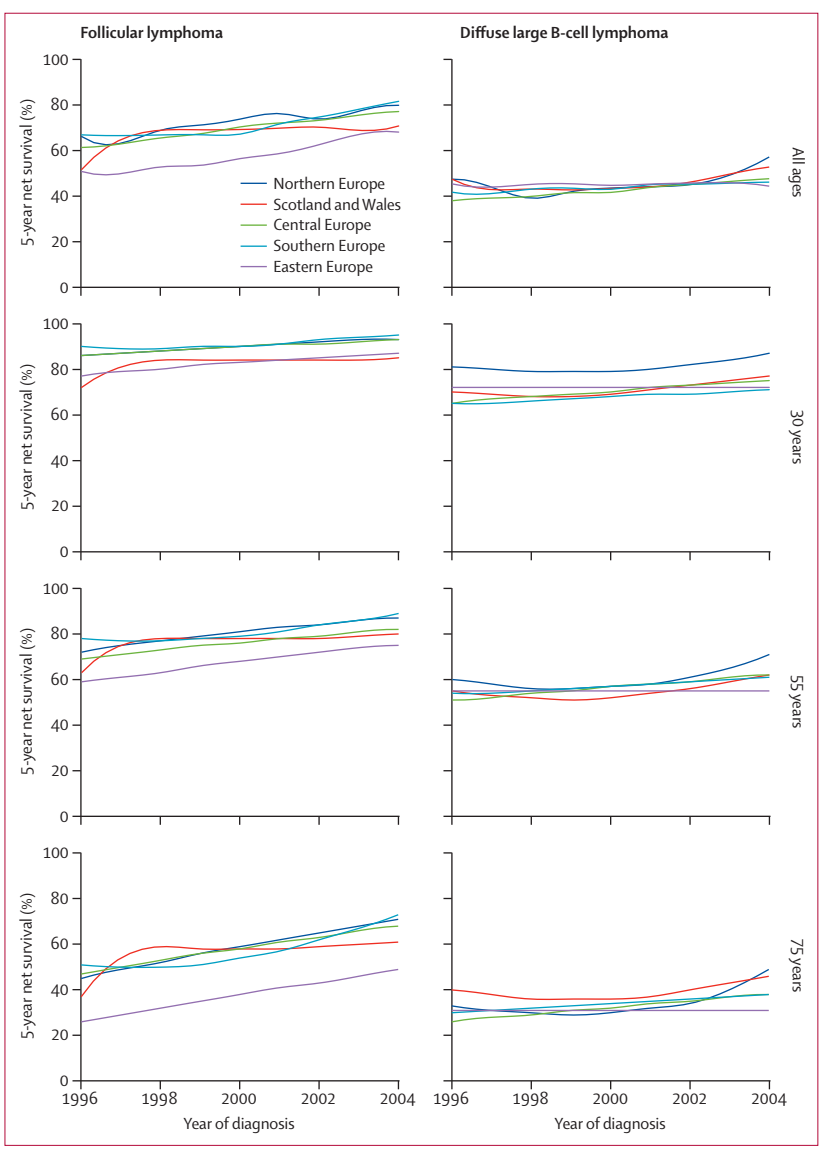

Figure 4: 5-year net survival probabilities according to the year of diagnosis in follicular lymphoma and diffuse large B-cell lymphoma

Figures 2 and 3 report the EMR according to time since diagnosis in follicular lymphoma (figure 2) and diffuse large B-cell lymphoma (figure 3) in each European area as estimated at 3 fixed years of (1996, 2000, and 2004) and three ages at (30 years, 55 years, and 75 years) diagnosis. In patients of all ages with follicular lymphoma, the EMR dynamic differed widely between areas (figure 2): in northern Europe, the EMR remained stable for 5 years after diagnosis, but in the other areas, especially eastern Europe, the EMR was high just after diagnosis. After 1 year, the EMRs were similar between areas and did not exceed 0·2 deaths per person-year. In patients aged 30 years, we noted a peculiar EMR dynamic in Scotland and Wales and eastern Europe, with an EMR fluctuating more with time since diagnosis compared with other areas. In patients aged 75 years, we noted high short-term mortality rates in all areas but northern Europe. The EMR decreased during the last years of diagnosis in all age classes and areas. In 1996, in Scotland and Wales and southern and eastern Europe, the EMR was higher than in the two other areas, but it decreased over time to reach similar values by 2004.

In patients of all ages with diffuse large B-cell lymphoma, the EMR dynamic was nearly the same in all areas; the high rates noted just after diagnosis decreased thereafter (figure 3). In patients aged 30 years, the mortality rates just after diagnosis were higher in central, southern, and eastern Europe than in northern Europe and Scotland and Wales. In patients aged 55 years, during the first year, the EMR was higher in eastern Europe than in the other areas; this difference was less marked in patients aged 75 years. The EMRs did not differ much according to the year of diagnosis: we noted no significant effect in eastern Europe, but in northern, central, and southern Europe, we noted a slight effect in

the last years of diagnosis. We noted a peculiar trend in Scotland and Wales: during the first year, the EMR was higher in 2004 than in 1996 whatever the age.

We estimated trends of the 5-year net survival according to the year of diagnosis as a continuous variable with area-specific and subtype-specific models at ages 30 years, 55 years, and 75 years (figure 4), which shows how the changes with year of diagnosis in the dynamics of EMR finally affect 5-year net survival. In follicular lymphoma, the net survival improved progressively in northern, central, and eastern Europe, with a significant effect (appendix p 9). In Scotland and Wales and southern Europe, the year of diagnosis had a significant non-linear effect on the EMR. In Scotland and Wales, the 5-year net survival increased until 1998 and stabilised thereafter. In southern Europe, the 5-year net survival started to increase after 2000. Despite these increases, the area disparity noted in figure 1 was also noted in figure 4: in patients that were 30 years old, net survival was lower in Scotland and Wales and eastern Europe than in northern, central, and southern Europe. In patients aged 55 years old and 75 years old, net survival in eastern Europe was lower than in the other areas (figure 4).

In diffuse large B-cell lymphoma, net survival increased slightly over the last years of diagnosis, except in eastern Europe. For this area, the slight increase seen in figure 4 for all ages shows a change in age structure over the years of diagnosis. In central and southern Europe, the year of diagnosis had a significant linear effect on the EMR (appendix p 9), but it had a non-linear effect on the EMR in Scotland and Wales and northern Europe, where the net survival improved significantly after 2002 for all ages. Survival disparities were more noticeable in patients aged 30 years; the prognosis was better in northern Europe than in the other areas.

Discussion

For follicular lymphoma, we showed higher net survival probabilities during the last years of diagnosis (2002–04) than in previous years in all areas and age groups, and a constant effect of the year of diagnosis on the EMR. For diffuse large B-cell lymphoma, net survival increased slightly during the study period, except in eastern Europe. Despite different statistical approaches and cohorts, these results agree with the previous EUROCARE-5 report on haematological malignancies[8] and other population-based studies,[18,19] substantiating the analyses' robustness and the European dataset's reliability. Unlike previous EUROCARE studies,[6,8] northern Europe data in this study relied essentially on the Norwegian cancer registry; however, non-Hodgkin lymphoma survival seems homogeneous in Nordic countries.[20] Similarly, the UK data in this study relied on Wales and Scotland, and did not include England, Ireland, and Northern Ireland; this calls for caution, although survival differences between these regions seem negligible.[21]

Several facts might explain the improvement of follicular lymphoma and diffuse large B-cell lymphoma survival during the last study years in all areas. First, progress in diagnosis and staging methods (ie, molecular markers, immunophenotyping, and imaging techniques) has led to improved diagnoses, classifications, disease extension assessments, and therapeutic decisions.[22] Second, use of a new drug (rituximab) for follicular lymphoma and diffuse large B-cell lymphoma in combination with conventional chemotherapies[4,5] and the wider recourse to autologous stem-cell transplantation in the youngest patients with relapse[23] has increased survival. Third, guidelines for daily practice[24,25] issued in most European countries (ie, rituximab and polychemotherapy for induction and maintenance) or so-called watchful waiting for follicular lymphoma with high tumour burden or diffuse large B-cell lymphoma has also been beneficial.

Nevertheless, age-related differences in prognosis still exist between European areas. Various studies have already reported poorer survival in elderly patients than in young patients.[1,6,8] In this study, we show more marked differences in southern Europe for follicular lymphoma and northern Europe for diffuse large B-cell lymphoma. Two explanations could be, first, differences in care provision or clinical practices (ie, more aggressive treatments in younger patients or suboptimum treatment in the elderly[26]), or, second, more inclusions of younger patients in clinical trials with shorter delays to treatment.[26]

Area-related differences in survival were expected and could have several major explanations: first, different paces in use of new drugs; second, absence of access to modern treatments in eastern Europe;[8] third, uneven guideline implementation or accuracy (eg, radiotherapy doses for follicular lymphoma stages I and II); and finally, optimum chemotherapy and costly and short lead-time treatments in the youngest patients (which reduces early mortality).[20] Other explanations could be different case mixes, suboptimum so-called wait and watch procedures, working in multidisciplinary teams,[27] different socioeconomic conditions and life habits, different health insurance schemes (which could delay diagnosis), or different HIV prevalence.[28] As in every survival study, another potential cause of differences in survival could be a non-comparability between disease incidence during the study period due to different sensitivities of the medical systems between areas, qualities of recording by cancer registries, and percentages of unspecified cases (table). In fact, a low follicular lymphoma or diffuse large B-cell lymphoma incidence might be attributable to non-detection of the most serious cases; the probability of survival would then be biased towards an overestimation.

For follicular lymphoma, the EMR was low and constant in northern Europe; however, we noted high EMRs during the first year after diagnosis in the other areas for follicular lymphoma and in all areas for diffuse

large B-cell lymphoma. Possible explanations for this finding could be long delays to treatment or access to aggressive treatments.

All of these assumptions need confirmation and detailed databases because the cancer registries do not routinely collect data for the following characteristics: first, lymphoma stage (an unequal repartition of stage during the study period would explain survival differences between European areas); second, cancer management (use of new drugs at various moments in several countries could be an explanation for these survival differences). The absence of data for treatment in the EUROCARE-5 database did not allow investigation of differences in therapeutic management in this study. We used the year of diagnosis as an indirect indicator of change in follicular lymphoma and diffuse large B-cell lymphoma therapeutic management over time in each European area. Finally, the cancer registries need improved recording of comorbidities and socioeconomic facts. Additionally, the period of diagnosis of our data did not allow us to assess recent advances in management of lymphoma (mainly, use of new drugs) or the effect of new prognostic indexes on practitioners' treatment decisions.

One asset and originality of our study is its estimation methods. First, Pohar-Perme's estimator provided unbiased punctual estimations of net survival, and age standardisation allowed comparisons with other European studies. The relative 5-year survival estimated with the Ederer II method were close to those estimated by the Pohar-Perme estimator;[29] hence, our results are close to previous EUROCARE-5 results.[8] Second, the flexible regression was essential to describe the EMR dynamics over the years of diagnosis. We focused our analysis on the dynamics of the EMR according to the year of diagnosis and age specifically in each European area, but did not compare survival and excess mortality rates between areas. Third, modelling with the year of diagnosis as a continuous variable allowed us to display curve changes, which are not obvious on figure 1. Our model-building strategy[17] allowed simultaneous consideration of the effects of the year of and age at diagnosis on the EMR, with possible non-linear or non-proportional effects for both covariates. We paid particular attention to the trend in expected mortality according to age at diagnosis in each cancer registry. Study of these trends by sex showed that variability was low according to the year of diagnosis and between areas (data not shown).

We focused our analysis on the effect of the year of and age at diagnosis on mortality, rather than on the effect of sex, which is less influential on patients' prognosis than is the year of and age at diagnosis. Modelling the additional effect of sex would need a far more complex modelling strategy than the one that we used and a specific study. We therefore showed results for all patients together.

This EUROCARE population-based study shows that despite international guidelines[24,25] and progress in health care, age-related differences in survival after follicular lymphoma or diffuse large B-cell lymphoma still exist between European areas. However, decreasing EMRs should foster the search for more and better means of improving access to modern care.

Contributors

RG, NB, MMa, LR, AB, and MMo designed the study. EUROCARE provided access to its European database. PM, RDA, RC, and MS extracted, pooled, and tabulated and organised data. MMo, NB, RG, LR, AB, MMa, PM, RDA, and RC analysed and interpreted data. MMo, RG, NB, AB, LR, MMa, PM, RDA, RC, MS, AM, XT, and JI wrote the report. All authors read and approved the final version of the manuscript.

Declaration of interests

All authors declare no competing interests.

References

1 Sant M, Allemani C, De Angelis R, et al, for the EUROCARE-3 Working Group. Influence of morphology on survival for non-Hodgkin lymphoma in Europe and the United States. *Eur J Cancer* 2008; **44:** 579–87.

2 Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer Press, 2001.

3 Fritz A, Percy C, Jack A, et al, eds. International Classification of Diseases for Oncology, 3rd edn. Geneva: World Health Organization, 2000.

4 Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346:** 235–42.

5 Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood* 2008; **112:** 4824–31.

6 De Angelis R, Sant M, Coleman MP, et al, for the EUROCARE-5 Working Group. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *Lancet Oncol* 2014; **15:** 23–34.

7 Marcos-Gragera R, Allemani C, Tereanu C, et al, for the HAEMACARE Working Group. Survival of European patients diagnosed with lymphoid neoplasms in 2000–2002: results of the HAEMACARE project. *Haematologica* 2011; **96:** 720–28.

8 Sant M, Minicozzi P, Mounier M, et al, for the EUROCARE-5 Working Group. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. *Lancet Oncol* 2014; **15:** 931–42.

9 Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. *Stat Med* 1990; **9:** 529–38.

10 Danieli C, Remontet L, Bossard N, Roche L, Belot A. Estimating net survival: the importance of allowing for informative censoring. *Stat Med* 2012; **31:** 775–86.

11 Roche L, Danieli C, Belot A, et al. Cancer net survival on registry data: use of the new unbiased Pohar-Perme estimator and magnitude of the bias with the classical methods. *Int J Cancer* 2013; **132:** 2359–69.

12 Perme MP, Stare J, Estève J. On estimation in relative survival. *Biometrics* 2012; **68:** 113–20.

13 Giorgi R, Abrahamowicz M, Quantin C, et al. A relative survival regression model using B-spline functions to model non-proportional hazards. *Stat Med* 2003; **22:** 2767–84.

14 Remontet L, Bossard N, Belot A, Estève J, for the French network of cancer registries FRANCIM. An overall strategy based on regression models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. *Stat Med* 2007; **26:** 2214–28.

15 Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 2004; **40:** 2307–16.

16 Bossard N, Velten M, Remontet L, et al. Survival of cancer patients in France: a population-based study from the Association of the French Cancer Registries (FRANCIM). *Eur J Cancer* 2007; **43:** 149–60.

17 Wynant W, Abrahamowicz M. Impact of the model-building strategy on inference about nonlinear and time-dependent covariate effects in survival analysis. *Stat Med* 2014; **33:** 3318–37.

18 Bosetti C, Bertuccio P, Malvezzi M, et al. Cancer mortality in Europe, 2005–2009, and an overview of trends since 1980. *Ann Oncol* 2013; **24:** 2657–71.

19 Monnereau A, Troussard X, Belot A, et al, for the French Network of Cancer Registries (FRANCIM). Unbiased estimates of long-term net survival of hematological malignancy patients detailed by major subtypes in France. *Int J Cancer* 2013; **132:** 2378–87.

20 Storm HH, Klint Å, Tryggvadóttir L, et al. Trends in the survival of patients diagnosed with malignant neoplasms of lymphoid, haematopoietic, and related tissue in the Nordic countries 1964–2003 followed up to the end of 2006. *Acta Oncol* 2010; **49:** 694–712.

21 Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971–2011: a population-based study. *Lancet* 2015; **385:** 1206–18.

22 Al-Hamadani M, Go RS. Stage redistribution and survival among Medicare beneficiaries before and after the approval of positron emission tomography scan for non-Hodgkin lymphoma. *Leuk Lymphoma* 2015; **56:** 1544–46.

23 Le Gouill S, De Guibert S, Planche L, et al, for GELA and GOELAMS. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. *Haematologica* 2011; **96:** 1128–35.

24 Hiddemann W, for the European Society for Medical Oncology. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphoma. *Ann Oncol* 2003; **14:** 1163–64.

25 ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of newly diagnosed large cell non-Hodgkin's lymphoma. *Ann Oncol* 2001; **12:** 1209–10.

26 Fields PA, Linch DC. Treatment of the elderly patient with diffuse large B cell lymphoma. *Br J Haematol* 2012; **157:** 159–70.

27 Munro AJ. Leukaemia and lymphoma: why has survival improved? *Lancet Oncol* 2014; **15:** 906–07.

28 Tao L, Foran JM, Clarke CA, Gomez SL, Keegan TH. Socioeconomic disparities in mortality after diffuse large B-cell lymphoma in the modern treatment era. *Blood* 2014; **123:** 3553–62.

29 Seppä K, Hakulinen T, Pokhrel A. Choosing the net survival method for cancer survival estimation. *Eur J Cancer* 2015; **51:** 1123–29.