EUROPEAN JOURNAL OF CANCER 44 (2008) 579–587

available at www.sciencedirect.com

journal homepage: www.ejconline.com

# Influence of morphology on survival for non-Hodgkin lymphoma in Europe and the United States

*Milena Sant[a], Claudia Allemani[a,*], Roberta De Angelis[b], Antonino Carbone[c], Silvia de SanJosè[d], Alessandro M. Gianni[e], Pilar Giraldo[f], Francesca Marchesi[a], Rafael Marcos-Gragera[g], Carmen Martos-Jiménez[h], Marc Maynadié[i], Martine Raphael[j], Franco Berrino[a], EUROCARE-3 Working Group[k]*

[a]*Department of Preventive and Predictive Medicine, Fondazione IRCCS 'Istituto Nazionale dei Tumori', Via Venezian 1, I-20133, Milan, Italy*
[b]*Department of Cancer Epidemiology, National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy*
[c]*Pathology Department, Fondazione IRCCS 'Istituto Nazionale dei Tumori', Milan, Italy*
[d]*Epidemiology and Cancer Registry, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain*
[e]*Leukaemia and lymphoma Department, Fondazione IRCCS 'Istituto Nazionale dei Tumori', Milan, Italy*
[f]*Department of Haematology, Hospital Universitario Miguel Servet, Zaragoza, Spain*

* *Corresponding author:* Tel.: +39 02 23903521/2901/2; fax: +39 02 23903516.
E-mail address: claudia.allemani@istitutotumori.mi.it (C. Allemani).

[k] The EUROCARE-3 Working Group is: Austria: W. Oberaigner (Tyrol Cancer Registry); Denmark: H.H. Storm (Danish Cancer Society, Department of Cancer Prevention and Documentation); Estonia: T. Aareleid (Estonian Cancer Registry); Czech Republic: M. Jechova, M. Rousarova (IHIS and West Bohemia Cancer Registry); Finland: T. Hakulinen (Finnish Cancer Registry); France: G. Hédelin (Bas-Rhin Cancer Registry), I. Tron, E. Le Gall (Bretagne Childhood Cancer Registry), G. Launoy (Calvados Digestive Cancer Registry), J. Macé-Lesec'h (Calvados General Cancer Registry), J. Faivre (Côte d'Or Digestive Cancer Registry), G. Chaplain (Côte d'Or Gynaecologic Cancer Registry), P.-M. Carli (Côte d'Or Malignant Haemopathies Registry), A. Danzon (Doubs Cancer Registry), B. Tretarre (Hérault Cancer Registry), M. Colonna (Isère Cancer Registry), B. Lacour (Lorraine Childhood Cancer Registry), N. Raverdy (Somme Cancer Registry), C. Berger, F. Freycon (Rhône-Alpes Childhood Registry), P. Grosclaude (Tarn Cancer Registry), J. Estève (University of Lyon); Germany: P. Kaatsch (German Childhood Cancer Registry), H. Ziegler (Saarland Cancer Registry), D. Hölzel, G. Schubert Fritschle (Munich Cancer Registry); Iceland: L. Tryggvadottir (Icelandic Cancer Registry); Italy: F. Berrino (Project Leader), C. Allemani, P. Baili, L. Ciccolallo, P. Crosignani, G. Gatta, A. Micheli, M. Sant, (Fondazione IRCCS 'Istituto Nazionale dei Tumori', Milan, Unit of Etiological Epidemiology and Prevention and Lombardy Cancer Registry, Varese Province) S. Ferretti (Ferrara Cancer Registry), E. Conti[l], V. Ramazzotti (Istituto Nazionale Tumori 'Regina Elena', Rome, Latina Cancer Registry), M. Vercelli, A. Quaglia (Liguria Region Cancer Registry, DOBIG University GE, IST Genova), F. Pannelli (Macerata Cancer Registry, Marche Childhood Cancer Registry), M. Federico, M.E. Artioli (Modena Cancer Registry), M. Ponz De Leon, P. Benatti (Modena Colorectal Cancer Registry), V. De Lisi, L. Servente (Parma Cancer Registry), R. Zanetti, S. Patriarca (Piedmont Cancer Registry), C. Magnani, G. Pastore (Piedmont Childhood Cancer Registry), L. Gafà, R. Tumino (Ragusa Cancer Registry), F. Falcini (Romagna Cancer Registry), M. Budroni (Sassari Cancer Registry), E. Paci, E. Crocetti (Tuscan Cancer Registry), P. Zambon, S. Guzzinati (Venetian Cancer Registry), R. Capocaccia, E. Carrani, R. De Angelis, P. Roazzi, M. Santaquilani, A. Tavilla, F. Valente, A. Verdecchia (Istituto Superiore di Sanità, Rome); Malta: M. Dalmas (Malta National Cancer Registry); Norway: F. Langmark, A. Andersen (Cancer Registry of Norway, Institute of Population-based Cancer Research); Poland: J. Rachtan (Cracow Cancer Registry), M. Bielska-Lasota, Z. Wronkowski (Warsaw Cancer Registry); Slovakia: I Pleško, A Obsitníková (National Cancer Registry of Slovakia); Slovenia: V. Pompe-Kirn (Cancer Registry of Slovenia); Spain: I. Izarzugaza (Basque Country Cancer Registry), C. Martinez-Garcia (Granada Cancer Registry), I. Garau (Mallorca Cancer Registry), C. Navarro, M.D. Chirlaque (Murcia Cancer Registry), E. Ardanaz, C. Moreno (Navarra Cancer Registry), J. Galceran (Tarragona Cancer Registry), A. Torrella (Childhood Tumor Registry of Valencia), R. Peris-Bonet (National Childhood Cancer Registry and Instituto Lopez Pinero, Valencia); Sweden: L. Barlow, T. Möller (Cancer Registry of Sweden); Switzerland: G. Jundt (Basel Cancer Registry), J.M. Lutz, M. Usel (Geneva Cancer Registry); The Netherlands: J.W.W. Coebergh (Eindhoven Cancer Registry), A. van der Does-van den Berg (Dutch Childhood Oncology Group), O. Visser (Amsterdam Cancer Registry); UK, England: S. Godward (East Anglian Cancer Registry), M.P. Coleman (London School of Hygiene and Tropical Medicine), E.M.I. Williams (Merseyside and Cheshire Cancer Registry), D. Forman (Northern and Yorkshire Cancer Registry and Information Service), M.J. Quinn (Office for National Statistics), M. Roche, S. Edwards (Oxford Cancer Intelligence Unit), C. Stiller (Childhood Cancer Research Group, Oxford), J. Verne (South West Cancer Intelligence Services), H. Møller, J. Bell (Thames Cancer Registry), J.L. Botha (Trent Cancer Registry), G. Lawrence (West Midlands Cancer Intelligence Unit); UK, Scotland: R. Black (Scottish Cancer Intelligence Unit); UK, Wales: J.A. Steward (Welsh Cancer Intelligence and Surveillance Unit).[l]Dr. Ettore Conti died on August 2, 2003.

0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2007.12.016

[g]Epidemiology Unit and Girona Cancer Registry, Institut Català d'Oncologia, Girona, Spain
[h]Department of Government of Aragon, Cancer Registry of Zaragoza, Health Zaragoza, Spain
[i]Côte d'Or Haematological Malignancies Registry, Dijon, France
[j]Department of Haematology, Centre Hospitalier Universitaire de Bicètre, Université Paris Sud, Le Kremlin-Bicêtre, France

ARTICLE INFO

*Article history:*
Received 16 November 2007
Received in revised form 20 December 2007
Accepted 21 December 2007
Available online 31 January 2008

*Keywords:*
EUROCARE
Non-Hodgkin's lymphoma
Population cancer registries
Survival
US SEER

ABSTRACT

We explored the influence of morphology on geographic differences in 5-year survival for non-Hodgkin lymphoma (NHL) diagnosed in 1990–1994 and followed for 5 years: 16,955 cases from 27 EUROCARE-3 cancer registries, and 22,713 cases from 9 US SEER registries. Overall 5-year relative survival was 56.1% in EUROCARE west, 47.1% in EUROCARE east and 56.3% in SEER. Relative excess risk (RER) of death was 1.05 (95% confidence interval (CI) 1.01–1.10) in EUROCARE west, 1.52 (95% CI 1.44–1.60) in EUROCARE east (SEER reference). Excess risk of death was significantly above reference (diffuse B lymphoma) for Burkitt's and NOS lymphoma; not different for lymphoblastic and other T-cell; significantly below reference (in the order of decreasing relative excess risk) for NHL NOS, mantle cell/centrocytic, lymphoplasmacytic, follicular, small lymphocytic/chronic lymphocytic leukaemia, other specified NHL and cutaneous morphologies.

Interpretation of marked variation in survival with morphology is complicated by classification inconsistencies. The completeness and standardisation of cancer registry morphology data needs to be improved.



## 1. Introduction

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoid cancers. Various classifications have been used in recent years, based on morphological and clinical features.[1–3] The recent World Health Organization (WHO) classification uses morphological, genetic immunohistochemical and clinical characteristics to classify NHL according to cell lineage of origin.[4] The evolving classification for NHL complicates comparisons of disease incidence and survival over time and across regions.[5]

For incidence and survival estimates, population-based cancer registries, particularly in Europe,[6,7] have considered NHL as a single disease entity, although some have taken account of morphology.[8] US population-based studies have considered distinct morphological groups, exploiting the morphological information available in the Surveillance, Epidemiology and End Results (SEER) database.[9]

The aims of the present study were (a) to test the feasibility of using the information on NHL morphology available in the EUROCARE dataset to evaluate the influence of NHL morphology on prognosis and (b) to compare survival for distinct morphologic subtypes across European countries and between Europe and the US.

## 2. Materials and methods

We analysed 16,955 NHL cases diagnosed in 1990–1994 in 27 of the 67 population-based cancer registries participating in EUROCARE-3,[10] and 22,713 NHL cases diagnosed over the same period in 9 US cancer registries (San Francisco-Oakland SMSA, Connecticut, Detroit-Metropolitan, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah and Atlanta-Metropolitan) available in the SEER public use database.[11] These datasets included 7982 cases (3785 in EUROCARE and 4197 in SEER) of chronic lymphocytic leukaemia (CLL). This entity is classified together with small lymphocytic NHL (SLL) in the 2001 WHO manual[4] and subsequently referred to as SLL/CLL. All cases were followed up for at least 5 years.

The EUROCARE-3 registries included in the study were those that provided information on morphology according to the second edition of the International Classification of diseases for Oncology (ICDO-2)[12] and had less than 40% of cases with not otherwise specified (NOS) morphology. These registries were grouped as EUROCARE west, consisting of registries from France, Germany, Italy, the Netherlands, Spain, Switzerland and the national registries of Iceland and Malta; and EUROCARE east, consisting of the national registries of the Czech Republic, Estonia, Slovakia and Slovenia. The populations of the SEER cancer registries were considered together.

Eight hundred and eighty cases (EUROCARE 554 (3.3%); SEER 326 (1.4%)) known to registries by death certificate only (DCO) or diagnosed only at autopsy were excluded from the survival analyses. The ICDO-2 morphology codes were grouped into 12 categories: diffuse B lymphoma (codes 9595, 9680–9684 and 9686); chronic lymphocytic leukaemia/small lymphocytic lymphoma (SLL/CLL) (codes 9670 and 9823); lymphoplasmacytic lymphoma (codes 9671 and 9715); lymphoblastic lymphoma (code 9685); Burkitt's lymphoma (code 9687); follicular lymphoma (codes 9675, 9676 and 9690–9698); cutaneous lymphoma (codes 9700, 9701 and 9709); mantle cell/centrocytic lymphoma (codes 9672–9674 and 9677); other T-cell lymphomas (codes 9702–9707, 9713, 9714 and 9720); other specified NHL (codes 9711 and 9712), NOS NHL (codes 9591–9593); and NOS lymphoma (codes 9590 and 9594).

Age at diagnosis was grouped into four categories: 0–14, 15–49, 50–69 and 70–99 years.

**Table 1 – Numbers of NHL cases contributed by the SEER and EUROCARE databases (the latter according to registry and geographic area) with quality indicators**

| Country/area | Registry | No. of cases | Lost to follow-up (%) | DCO/autopsy (%) | Microscopically verified (%) | All NOS[d] (%) |
|---|---|---|---|---|---|---|
| France | Bas-Rhin | 723 | 0.8 | 0.1 | 96.7 | 36.1 |
| | Calvados | 364 | 0.0 | 0.0 | 92.9 | 11.3 |
| Germany | Saarland | 834 | 0.0 | 4.2 | 93.7 | 23.5 |
| Iceland | ICELAND[b] | 131 | 0.0 | 0.8 | 100.0 | 22.1 |
| Italy | Ferrara | 477 | 1.1 | 1.7 | 98.5 | 37.1 |
| | Genoa | 793 | 0.0 | 1.5 | 88.9 | 11.6 |
| | Latina | 249 | 0.0 | 4.0 | 90.4 | 32.5 |
| | Modena | 780 | 4.1 | 2.0 | 97.4 | 21.8 |
| | Parma | 440 | 0.0 | 0.7 | 97.6 | 24.8 |
| | Ragusa | 181 | 0.0 | 1.1 | 96.7 | 35.9 |
| | Sassari | 197 | 1.5 | 0.0 | 95.9 | 11.7 |
| | Turin | 872 | 1.6 | 2.5 | 96.1 | 29.0 |
| | Varese | 776 | 0.4 | 0.9 | 97.6 | 34.4 |
| Malta | MALTA[b] | 92 | 0.0 | 1.1 | 97.8 | 30.4 |
| The Netherlands | Amsterdam | 2002 | 0.0 | 0.7 | 100.0 | 15.4 |
| | Eindhoven | 563 | 0.0 | 0.0 | 98.2 | 19.4 |
| Spain | Basque Country | 1311 | 0.0 | 5.9 | 94.1 | 28.6 |
| | Granada | 188 | 1.6 | 1.1 | 96.8 | 25.5 |
| | Mallorca | 357 | 1.1 | 0.6 | 97.5 | 32.8 |
| | Navarra | 369 | 0.0 | 5.1 | 95.7 | 19.0 |
| | Tarragona | 376 | 0.0 | 2.4 | 97.3 | 37.8 |
| Switzerland | Basel | 214 | 2.3 | 0.0 | 100.0 | 25.2 |
| | Geneva | 352 | 4.0 | 5.1 | 97.7 | 23.0 |
| **EUROCARE west[a]** | | **12,652** | **0.7** | **2.0** | **96.4** | **24.5** |
| Czech Republic | CZECH[b] | 542 | 0.0 | 8.1 | 95.7 | 19.6 |
| Estonia | ESTONIA[b] | 674 | 0.5 | 3.0 | 99.1 | 19.7 |
| Slovakia | SLOVAKIA[b] | 2020 | 0.0 | 10.5 | 95.9 | 20.5 |
| Slovenia | SLOVENIA[b] | 1067 | 0.8 | 1.8 | 98.4 | 30.7 |
| **EUROCARE east[a]** | | **4303** | **0.3** | **6.9** | **97.0** | **22.8** |
| **EUROCARE overall** | | **16,955** | **0.6** | **3.3** | **96.5** | **24.1** |
| **USA[c]** | SEER | **22,713** | **0.0** | **1.4** | **96.2** | **13.1** |

*Abbreviations*: DCO, death certificate only; NOS, not otherwise specified.
a Categories in bold incorporate the previously listed cancer registries.
b Registries in capital letters cover the whole country.
c USA SEER registries of San Francisco-Oakland SMSA, Connecticut, Detroit-Metropolitan, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah and Atlanta-Metropolitan.
d Includes NOS known to be NHL and NOS known to be lymphoma.

Five-year relative survival was estimated by the Hakulinen method[13] with 95% confidence intervals (CI) calculated from the standard error according to Greenwood's method.[14] Relative survival is an estimate of the probability of cancer survival after adjusting for competing causes of death determined from general population life tables, specific for each country or registry. For Europe, general population life tables, specific for each country or registry area, were used. For the USA, only race/ethnicity-specific national life tables were available in the SEER dataset. To obtain a national life table for all races/ethnicities, we weighted the race/ethnicity-specific national life tables according to the proportions of Whites, Blacks and Others (SEER terminology) present in the SEER NHL cases.

Differences in 5-year relative survival by geographical area were modelled using a multiple regression approach based on generalised linear models and adopting the Poisson assumption for the observed number of deaths.[15] The relative excess risks (RERs) of death derived from these models quantified the extent to which the risk of death in a given group differed from that in the reference category, after taking into account the background risk of death in the general population of each country or region.

## 3. Results

Table 1 shows the total number of US cases, and the total number of European cases by registry and geographic area, with quality indicators as percentages: lost to follow-up, discovered at autopsy/DCO, microscopically confirmed and NOS (NHL or lymphoma). Lost to follow-up cases were 0.7% (range 0.0–4.1%) in EUROCARE west, 0.3% (range 0.0–0.8%) in EUROCARE east, 0.6% in EUROCARE overall and 0.0% in SEER. Autopsy/DCO cases were 2.0% (range 0.0–5.9%) in EUROCARE west, 6.9% (range 1.8–10.5%) in EUROCARE east, 3.3% in EUROCARE overall and 1.4% in SEER.

Microscopically verified cases were 96.4% (range 88.9–100.0%) in EUROCARE west, 97.0% (range 95.7–99.1%) in EUROCARE east, 96.5% in EUROCARE overall and 96.2% in SEER.

**Table 2 – Distribution (%) of NHL morphological groups by country (European) and geographic grouping**

| Country | Morphological group | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | Lympho-blastic | SLL/CLL | Lym-phoplasmacytic | Follicular | Mantle cell/ centrocytic | Diffuse B | Burkitt's | Cutaneous | Other T-cell | Other specified NHL | NOS NHL | NOS lymphoma |
| France | 1087 | 1.3 | 26.5 | 3.0 | 19.1 | 2.7 | 17.0 | 1.3 | 0.5 | 0.9 | 0.0 | 2.9 | 24.8 |
| Germany | 834 | 1.2 | 21.6 | 8.0 | 16.9 | 2.2 | 19.0 | 2.3 | 1.0 | 3.9 | 0.4 | 16.4 | 7.1 |
| Iceland | 131 | 0.8 | 22.1 | 3.0 | 20.6 | 11.5 | 16.8 | 0.8 | 2.3 | 0.0 | 0.0 | 12.2 | 9.9 |
| Italy | 4776 | 0.6 | 23.0 | 8.0 | 13.5 | 5.0 | 19.4 | 0.9 | 3.0 | 0.5 | 0.2 | 18.3 | 7.6 |
| Malta | 92 | 1.1 | 28.3 | 0.0 | 14.1 | 2.2 | 18.5 | 0.0 | 4.3 | 1.1 | 0.0 | 17.4 | 13.0 |
| Netherlands | 2565 | 0.1 | 18.7 | 4.9 | 23.3 | 6.6 | 22.7 | 1.4 | 2.0 | 4.0 | 0.0 | 13.7 | 2.6 |
| Spain | 2601 | 0.3 | 24.5 | 3.2 | 15.5 | 7.4 | 14.4 | 2.3 | 2.8 | 0.7 | 0.0 | 15.8 | 13.1 |
| Switzerland | 566 | 0.5 | 22.2 | 9.4 | 18.9 | 4.6 | 18.2 | 1.4 | 0.7 | 0.2 | 0.0 | 7.1 | 16.8 |
| **EUROCARE west** | **12,652** | **0.5** | **22.6** | **5.9** | **17.0** | **5.4** | **18.7** | **1.5** | **2.3** | **1.5** | **0.1** | **14.9** | **9.6** |
| Czech Republic | 542 | 1.3 | 27.1 | 4.8 | 19.6 | 8.3 | 16.4 | 0.7 | 1.5 | 0.6 | 0.2 | 8.1 | 11.4 |
| Estonia | 674 | 0.0 | 51.8 | 0.9 | 4.0 | 20.3 | 1.3 | 0.0 | 1.2 | 0.7 | 0.0 | 5.1 | 14.7 |
| Slovakia | 2020 | 0.4 | 37.8 | 5.4 | 10.5 | 5.7 | 15.7 | 1.8 | 1.8 | 0.4 | 0.0 | 13.3 | 7.2 |
| Slovenia | 1067 | 0.8 | 31.8 | 3.9 | 5.1 | 2.2 | 17.0 | 0.8 | 0.5 | 4.1 | 3.2 | 25.4 | 5.2 |
| **EUROCARE east** | **4303** | **0.6** | **37.1** | **4.2** | **9.3** | **7.5** | **13.8** | **1.2** | **1.3** | **1.4** | **0.8** | **14.4** | **8.4** |
| **EUROCARE overall** | **16,955** | **0.5** | **26.3** | **5.5** | **15.0** | **5.9** | **17.5** | **1.4** | **2.1** | **1.5** | **0.3** | **14.7** | **9.3** |
| **USA SEER** | **22,713** | **0.9** | **24.8** | **0.7** | **18.2** | **4.4** | **32.6** | **1.0** | **2.9** | **1.2** | **0.2** | **1.8** | **11.3** |

*Abbreviations:* NHL, non-Hodgkin lymphoma; SLL/CLL, chronic lymphocytic leukaemia/small lymphocytic NHL; NOS, not otherwise specified.

Most autopsy/DCO cases were autoptic and hence microscopically verified.

Cases with NOS morphology (NHL or lymphoma) constituted 24.5% (range 11.3–37.8%) of EUROCARE west, 22.8% (range 19.6–30.7%) of EUROCARE east, 24.1% of EUROCARE overall and 13.1% of SEER cases.

Table 2 shows the total number of cases in each country and geographic grouping, together with the distribution (percentages) of morphological categories. The proportion of NOS NHL cases differed markedly between EUROCARE (14.7%) and SEER (1.8%); there was also a marked variation across Europe, ranging from 2.9% in France to 25.4% in Slovenia. By contrast, the proportions of NOS lymphoma cases differed much less (9.3% in EUROCARE versus 11.3% in SEER). All NOS cases formed 24.1% and 13.1%, respectively, of the EUROCARE and SEER datasets (Table 1).

Another major difference between the EUROCARE and SEER datasets concerned the proportions of diffuse B and lymphoplasmacytic morphologies. Diffuse B lymphoma was considerably less common in EUROCARE than in SEER (17.5% versus 32.6% of total cases; 23.0% versus 37.0% of cases with specified morphology), while lymphoplasmacytic was more common in EUROCARE than in SEER (5.5% versus 0.7% of total cases; 7.0% versus 0.8% of cases with specified morphology). Furthermore, while the variation in the frequency of diffuse B lymphoma across Europe was contained (range 14.4–22.7%; except Estonia with only 1.3%), the frequency of lymphoplasmacytic lymphoma varied considerably in the range from 0.0% (Malta) to 9.4% (Switzerland).

Overall frequencies of follicular lymphoma were similar in EUROCARE and SEER (15.0% versus 18.2% of total cases; 20.0% versus 21.0% of cases with specified morphology), with higher percentages (closer to SEER) in EUROCARE west (17.0%) than in EUROCARE east (9.3%), and with Slovenia (5.1%) and Estonia (4.0%) showing markedly lower percentages of this morphology than other countries. SLL/CLL frequency was similar in EUROCARE overall and SEER (26.3% versus 24.8% of total cases) but higher in EUROCARE east (37.1%).

The frequencies of less common NHL such as lymphoblastic and Burkitt's were similar in EUROCARE and SEER, and did not vary greatly between European countries. Mantle cell lymphoma also had similar frequencies in EUROCARE overall and SEER (5.9% versus 4.4% of total cases), but a much higher frequency in Estonia (20.3%). The frequency of cutaneous lymphoma was similar in EUROCARE and SEER (2.1% versus 2.9% of total cases), and had a uniform distribution across Europe, where most frequencies were below 4.0% (the exception of Malta is based on four cases). Likewise, the frequencies of the category other specified NHL were similar in SEER and EUROCARE, and there was no major variation across EUROCARE countries, except that Slovenia had a high frequency (3.2%) of this disease type.

Table 3 shows the distribution of morphological groups by age in the EUROCARE and SEER datasets. Lymphoblastic lymphoma was much less common in EUROCARE than in SEER (5.0% versus 24.5%) in the 0–14 year age category and to a lesser extent (1.1% versus 2.2%) in the 15–49 age category. Diffuse B lymphoma was less common in EUROCARE than in SEER in all age groups, the most remarkable difference being for age 0–14 (8.6% versus 23.7%). Mantle cell/centrocytic was much

**Table 3 – Distribution (%) of morphological groups by age in the EUROCARE and SEER datasets**

| Morphological group | Age (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0–14 | | 15–49 | | 50–69 | | 70–99 | |
| | EUROCARE | SEER | EUROCARE | SEER | EUROCARE | SEER | EUROCARE | SEER |
| Lymphoblastic | 5.0 | 24.5 | 1.1 | 2.2 | 0.3 | 0.3 | 0.3 | 0.2 |
| SLL/CLL | 2.7 | 1.8 | 9.7 | 8.5 | 29.0 | 27.4 | 32.1 | 32.2 |
| Lymphoplasmacytic | 0.0 | 0.9 | 3.7 | 0.6 | 5.9 | 0.7 | 6.1 | 0.7 |
| Follicular | 3.9 | 3.6 | 19.6 | 18.0 | 16.3 | 21.3 | 11.9 | 15.7 |
| Mantle cell/centrocytic | 15.6 | 0.4 | 6.3 | 2.6 | 6.1 | 5.4 | 5.2 | 4.6 |
| Diffuse B | 8.6 | 23.7 | 22.2 | 42.0 | 17.0 | 29.4 | 16.1 | 30.4 |
| Burkitt's | 28.4 | 29.0 | 3.4 | 2.4 | 0.5 | 0.4 | 0.3 | 0.1 |
| Cutaneous | 0.0 | 0.9 | 2.7 | 3.6 | 2.1 | 3.2 | 1.9 | 2.2 |
| Other T-cell | 10.9 | 4.5 | 2.4 | 1.8 | 1.2 | 1.1 | 1.0 | 1.1 |
| Other specified NHL | 1.2 | 0.0 | 0.4 | 0.2 | 0.3 | 0.3 | 0.2 | 0.1 |
| NOS NHL | 16.3 | 2.2 | 18.6 | 2.5 | 12.7 | 1.5 | 15.0 | 1.7 |
| NOS lymphoma | 7.4 | 8.5 | 9.9 | 15.6 | 8.6 | 9.0 | 9.9 | 11.1 |
| Totals | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Total number of cases | 257 | 224 | 3062 | 5145 | 7024 | 8325 | 6612 | 9019 |

*Abbreviations*: NHL, non-Hodgkin lymphoma; SLL/CLL, chronic lymphocytic leukaemia/small lymphocytic NHL; NOS, not otherwise specified.

commoner in the youngest (0–14 year) EUROCARE age group than in the corresponding SEER age group (15.6% versus 0.4%). Follicular lymphoma and SLL/CLL had similar frequencies at each age in both datasets, with SLL/CLL increasing in frequency with advancing age in both datasets. Burkitt's also had similar frequencies in both data sets, and was commonest in the youngest age group, to decrease in frequency with advancing age. Cutaneous lymphoma was slightly less common in EUROCARE than in SEER at all ages, while other T-cell lymphomas were much more common in EUROCARE than in SEER in the youngest (0–14 years) age group (10.9% versus 4.5%). NOS NHL was more common in EUROCARE than in SEER in all age groups, whereas NOS lymphoma was slightly more common in SEER in all age categories.

Fig. 1 shows 5-year relative survival and 95% CI, in the EUROCARE groupings and SEER, for all NHL combined and for each morphological group. Overall survival was 56.1% in EUROCARE west, 47.1% in EUROCARE east and 56.0% in SEER.

The morphologies with the highest survival were cutaneous lymphoma, and other specified lymphoma, followed by SLL/CLL, follicular lymphoma and lymphoplasmacytic lymphoma.

Morphologies with low survival were lymphoblastic, diffuse B, other T cell, Burkitt's and mantle cell/centrocytic. Survival for NOS NHL and NOS lymphoma was on the lower side, close to that of the morphologies with poorer prognoses.

For each morphological group, survival did not usually differ significantly between the three geographic groupings. Exceptions were cutaneous lymphoma, follicular lymphoma, SLL/CLL and mantle cell/centrocytic lymphoma, for which 5-year survival in EUROCARE east was significantly lower than in SEER; for follicular lymphoma, survival was also significantly lower in EUROCARE west than in SEER.

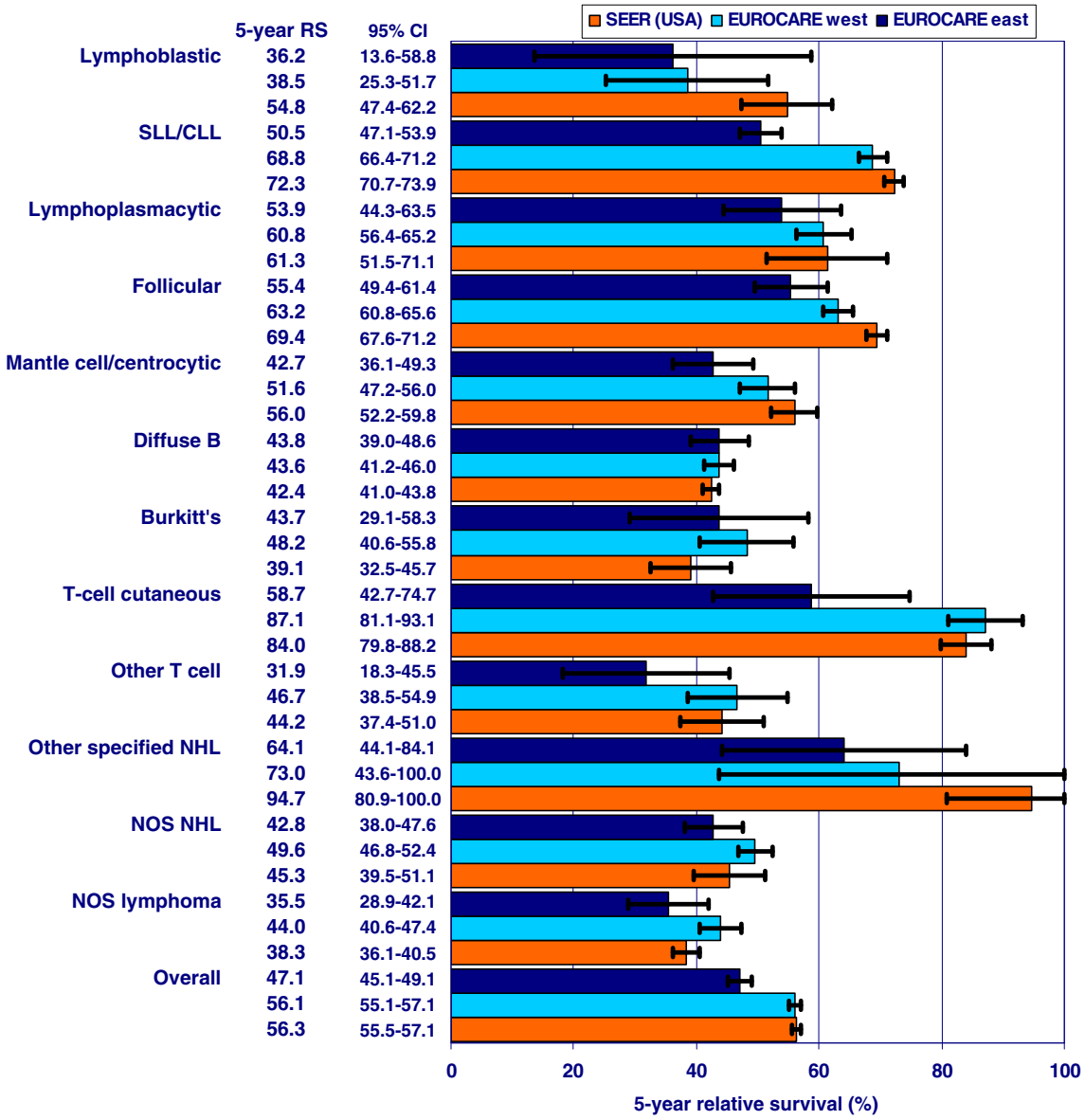
Table 4 shows 5-year RERs of death by geographic area adjusted by years since diagnosis, age at diagnosis and sex (model 1), and by morphology (model 2), with SEER as reference category. From model 1, the excess risk of death was significantly higher than reference for EUROCARE east (1.38; 95% CI 1.32–1.46) and was indistinguishable from reference for EUROCARE west (1.03; 95% CI 0.99–1.07). The RER of death was highest in the first year after diagnosis (reference category) and decreased to 0.18 (95% CI 0.17–0.20) in the fifth year.

The excess risk of death was lowest in the 0–14 year age group (0.60; 95% CI 0.50–0.71) and highest in the 15–49 year (1.23; 95% CI 1.18–1.29) and 70–99 year (1.73; 95% CI 1.67–1.80) age groups compared to the 50–69 year age group (reference category). The excess risk of death was 20% lower in females (0.80; 95% CI 0.78–0.83) than in males.

When morphological groups were included in the model (model 2), the RERs of death increased in EUROCARE east and increased slightly in EUROCARE west to become just significant. The RER of death for years since diagnosis and sex were similar to those obtained with model 1. The RER of death for patients aged 15–49 years in model 1 reduced in model 2 to become non-significant, and changed little in the other two age groups (0–14 and 70–99 years). Model 2 revealed significantly higher excess risk of death for Burkitt's and NOS lymphoma compared to diffuse B lymphoma (the commonest NHL chosen as reference) and significantly lower excess risk for the SLL/CLL, follicular lymphoma, mantle cell/centrocytic and cutaneous morphologies, as well as for other specified NHL and NHL NOS.

## 4. Discussion

We found that the survival of NHL patients diagnosed in 1990–1994 in EUROCARE west was similar to that in SEER patients, and higher than that in EUROCARE east. In the multivariable analysis adjusted by age and sex, differences in overall death risk between the three geographic areas were modest, but became more pronounced after adjustment for morphology, suggesting that not adjusting for morphology results in underestimation of differences. We found similar geographic variations in survival in our study of Hodgkin's lymphoma.[16] The significantly higher risk of death in EUROCARE east




Abbreviations: NHL, non-Hodgkin lymphoma; SLL/CLL, chronic lymphocytic leukemia/small lymphocytic NHL; NOS, not otherwise specified.

**Fig. 1 – Five-year relative survival (RS) by morphological group in EUROCARE west, EUROCARE east and SEER.**

may be due to inadequate access to or availability of appropriate treatments in the eastern European countries considered.

However, the results of our analyses according to morphological subtype revealed a number of anomalies. These were expected because of the known problem of poor comparability of population-based morphology data, particularly for a heterogeneous entity like NHL.[5,17–19] It is for this reason that an important aim of the present study was to assess whether it is possible to use the morphology data available in EUROCARE to evaluate its influence on prognosis.

Morphology registration by cancer registries is not always accurate[18] and this problem is compounded by the evolution of NHL classification in recent decades.[1–3,5] An additional problem may arise as a result of uncritical conversion from an older coding system to a newer coding system (e.g. from ICDO-1 to ICDO-2). In an attempt to overcome some of these problems, we grouped the ICDO-2 codes, provided by cancer registries, as far as possible according to the WHO classification[4] – based on ICDO-3[20] – and on the proposals of the InterLymph consortium.[21] However, it was not possible to perform a centralised pathological revision for reasons of cost.[17]

Other measures we took to improve data comparability were to include only cancer registries that coded according to ICDO-2 and those that had <40% of cases with unspecified morphology. These conditions resulted in the exclusion of approximately half the EUROCARE-3 registries, immediately uncovering an urgent need to improve standardisation within EUROCARE. Adoption of ICDO-3 codes together with the implementation of coding checks for haematological malignancies should improve data standardisation and quality.

**Table 4 – Relative excess risks (RERs) of death by country adjusted by years after diagnosis, age at diagnosis, sex (model 1) and morphological group (model 2)**

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | RER | 95% CI | RER | 95% CI |
| *Area* | | | | |
| USA SEER | **1** | | **1** | |
| EUROCARE west | **1.03** | 0.99–1.07 | **1.05** | 1.01–1.10 |
| EUROCARE east | **1.38** | 1.32–1.46 | **1.52** | 1.44–1.60 |
| *Follow-up* | | | | |
| Up to 1 year | **1** | | **1** | |
| 1–2 years | **0.33** | 0.32–0.35 | **0.35** | 0.33–0.36 |
| 2–3 years | **0.23** | 0.22–0.25 | **0.24** | 0.22–0.25 |
| 3–4 years | **0.19** | 0.18–0.20 | **0.19** | 0.17–0.20 |
| 4–5 years | **0.18** | 0.17–0.20 | **0.18** | 0.16–0.19 |
| *Age (years)* | | | | |
| 0–14 | **0.60** | 0.50–0.71 | **0.32** | 0.26–0.39 |
| 15–49 | **1.23** | 1.18–1.29 | **1.02** | 0.98–1.07 |
| 50–69 | **1** | | **1** | |
| 70–99 | **1.73** | 1.67–1.80 | **1.75** | 1.68–1.82 |
| *Sex* | | | | |
| M | **1** | | **1** | |
| F | **0.80** | 0.78–0.83 | **0.79** | 0.77–0.82 |
| *Morphological group* | | | | |
| Lymphoblastic | | | **1.02** | 0.86–1.21 |
| SLL/CLL | | | **0.32** | 0.30–0.34 |
| Lymphoplasmacytic | | | **0.45** | 0.41–0.51 |
| Follicular | | | **0.40** | 0.38–0.42 |
| Mantle cell/centrocytic | | | **0.59** | 0.55–0.64 |
| Diffuse B | | | **1** | |
| Burkitt's | | | **1.66** | 1.46–1.89 |
| Cutaneous | | | **0.16** | 0.13–0.20 |
| Other T-cell | | | **0.97** | 0.86–1.10 |
| Other specified NHL | | | **0.25** | 0.15–0.42 |
| NOS NHL | | | **0.81** | 0.76–0.86 |
| NOS lymphoma | | | **1.10** | 1.05–1.16 |

*Abbreviations*: NHL, non-Hodgkin lymphoma; SLL/CLL, chronic lymphocytic leukaemia/small lymphocytic NHL; NOS, not otherwise specified.

Turning now to examine the results of our analyses by morphology, we found that NOS NHL were much more common in EUROCARE than in SEER (15.0% versus 2.0%), suggesting at first sight that diagnostic accuracy is lower, or diagnosis reporting less complete, in EUROCARE. However, EUROCARE had a much lower frequency of diffuse B lymphoma than in SEER (18.0% versus 33.0%) suggesting that much of the difference in NOS NHL frequency may be attributable to differences in classification practice, and specifically that many cases considered NOS NHL in EUROCARE are considered diffuse by SEER. A recent population-based study emphasised the difficulties in diagnosing high grade lymphomas (including the diffuse B subtype), reporting only moderate agreement of recorded diagnoses with expert pathological review.[19]

Similar differences in classification practice between EUROCARE and SEER may also explain the greater frequency of the rarer lymphoplasmacytic lymphoma in the EUROCARE dataset (Table 2).

The much greater frequency of mantle cell/centrocytic lymphoma in EUROCARE children aged 0–14 years than SEER children (15.6% versus 0.4%; Table 3) indicates an anomaly in the EUROCARE data since mantle cell lymphoma is known to be rare in children.[8,22] Examination showed that the problem was mainly confined to Estonia, Slovakia and Spain, and could be due to uncritical coding conversion: the old ICDO-1 code 9630 included lymphoblastic lymphoma (quite common in children) as well as various types of mantle cell/centrocytic lymphoma.

The distinctive Burkitt's lymphoma had similar frequencies in the EUROCARE and SEER datasets, and was more frequent in the youngest age class than in the older classes, in accordance with the literature data.[8,22] By contrast, the much lower frequency of lymphoblastic lymphoma in EUROCARE in the age category 0–14 years (5.0% versus 24.5%), together with the low frequency in the 15–49 year age category, suggests that this morphology was generally distinguished from acute lymphoblastic leukaemia in EUROCARE during the study period (1990–1994) but not in SEER. Lymphoblastic lymphoma and lymphoblastic leukaemia are considered to have the same lineage.[4]

With regard to data comparability within the EUROCARE dataset, for Estonia we found low frequencies of diffuse and follicular types, very high frequency of mantle cell/centrocytic lymphoma and relatively high frequency of NOS lymphoma. These results show that classification or coding in Estonia differs markedly from that in the rest of EUROCARE,

either because of low reporting accuracy or low diagnostic accuracy. Similar considerations apply to the low frequency of follicular lymphoma in Slovenia.

It is therefore evident that the comparability of diagnosis of some NHL subtypes was low. Nevertheless, for morphologies where comparability was satisfactory, the results of the survival analyses were largely in agreement with the existing literature data. In particular, cutaneous lymphoma,[23] SLL/CLL and follicular lymphoma[24,25] had the best prognoses. By contrast, lymphoblastic lymphomas (which are often T-cell rather than B-cell derived)[4] had poor prognoses.[22,26]

The greater excess risk of death in men compared to women diagnosed with NHL is consistent with the well-documented finding that survival for many cancers is better in women than in men,[27] and may be due to earlier diagnosis, less comorbidity or better tolerance of treatment in women.[27,28] Since smoking and alcohol consumption have been associated with worsened prognosis for lymphoid malignances,[29] the lower prevalence of these habits in women may in part explain the phenomenon. It has also been suggested that the higher prevalence of HIV infection in men could contribute to their worse survival.[30] However, recent studies indicate that prognosis is similar in HIV positive and negative patients, for the same treatment, anatomical site localisation and stage.[30,31]

Tumour stage at diagnosis, which influences treatment response,[32] was not uniformly available or standardised across EUROCARE registries, and could not be taken into account in the present study. Similarly, treatment was not uniformly available, and when it was, it consisted only of summary information (such as whether chemo- or radiotherapy was given). Other prognostic factors known to influence NHL prognosis (performance status, B symptoms, bone marrow involvement, serum lactate dehydrogenase)[32,33] were not specified by the study protocol.

To conclude, although our study shows that cancer registries have the potential to provide morphology data to permit population-based evaluation of the influence of morphology on survival, the availability and standardisation of morphology data are insufficient, and it is important that EUROCARE registries adopt updated classifications of haematological malignancies consistent with those used in clinical and research settings.

## Research support

This study was supported by the foundation Compagnia di San Paolo, Turin, Italy and the HAEMACARE project funded by the European Commission.

## Conflict of interest statement

None declared.

## Acknowledgements

The authors thank Don Ward for helping with the English, Dr. Charles Stiller for critical comments on an earlier version of the manuscript and Chiara Margutti and Samba Sowe for secretarial assistance.

## REFERENCES

1. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1994;**49**:2112–35.
2. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;**84**:1361–92.
3. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 1997;**89**:3909–18.
4. Jaffe ES, Harris LN, Stein H, Vardiman JW, editors. *World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues, International Agency for Research on Cancer*. Lyon: (IARC) Press; 2001.
5. Clarke CA, Undurraga DM, Harasty PJ, Glaser SL, Morton EA, Holly EA. Changes in cancer registry coding for lymphoma subtypes: reliability over time and relevance for surveillance and study. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:630–8.
6. Carli PM, Coebergh JW, Verdecchia A. Variation in survival of adult patients with haematological malignancies in Europe since 1978. *Eur J Cancer* 1998;**34**:2253–63.
7. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94 – results and commentary. *Ann Oncol* 2003;**14**(Suppl. 5):61–118.
8. Cartwright R, Brincker H, Carli PM, Clayden D, Coebergh JW, Jack A, et al. The rise in incidence of lymphomas in Europe 1985–1992. *Eur J Cancer* 1999;**35**:627–33.
9. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* 2000;**92**:1240–51.
10. Berrino F, Capocaccia R, Coleman MP, Estève J, Gatta G, Hakulinen T, et al. Survival of cancer patients in Europe: The EUROCARE-3 Study. *Ann Oncol* 2003;**14**(Suppl. 5):1–155.
11. US Department of Health and Human Services. National Cancer Institute, Surveillance, epidemiology and end results program. SEER Cancer Statistics Review, 1973–1999 [Dataset on CDROM]. Bethesda (MD): US Department of Health and Human Services; 2001.
12. Percy C, Van Holten V, Muir C, editors. *International classification of diseases for oncology*. 2nd ed. Geneva: World Health Organization; 1990.
13. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics* 1982;**38**:933–42.
14. Greenwood M. The errors of sampling of the survivorship table. *Reports on Public Health and Medical Subjects*, vol. 33. Her Majesty's Stationery Office: London; 1926.
15. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**:51–64.
16. Allemani C, Sant M, De Angelis R, Marcos-Gragera R, Coebergh JW. EUROCARE Working Group. Hodgkin disease survival in Europe and the U.S.: prognostic significance of morphologic groups. *Cancer* 2006;**107**:352–60.
17. Turner JJ, Hughes AM, Kricker A, Milliken S, Grulich A, Kaldor J, et al. Use of the WHO lymphoma classification in a

population-based epidemiological study. *Ann Oncol* 2004;**15**:617–31.
18. Phekoo K, Møller H, Richards M, Schey S. Comparison of a specialist haematological malignancy database against a regional cancer registry: case ascertainment and diagnostic accuracy. *Br J Haematol* 2004;**119**:697–705.
19. Clarke CA, Glaser SL, Dorfman RF, Bracci PM, Eberle E, Holly EA, et al. Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: reliability of diagnosis and subtype classifications. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:138–43.
20. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al., editors. *International classification of diseases for oncology*. 3rd ed. Geneva: World Health Organization; 1990.
21. Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, Clarke CA, et al. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 2007;**110**:695–708.
22. Izarzugaza MI, Steliarova-Foucher E, Martos MC, Martos MC, Zivkovic S. Non-Hodgkin's lymphoma incidence and survival in European children and adolescents (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;**42**:2050–63.
23. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO–EORTC classification for cutaneous lymphomas. *Blood* 2005;**105**:3768–85.
24. Swenson WT, Wooldridge JE, Lynch CF, Forman-Hoffman VL, Chrischilles E, Link BK. Improved survival of follicular lymphoma patients in the United States. *J Clin Oncol* 2005;**23**:5019–26.
25. Winter JN, Gascoyne RD, Van Besien K. Low-grade lymphoma. *Hematology Am Soc Hematol Educ Program* 2004:203–2020.
26. Le Gouill S, Lepretre S, Brière J, Morel P, Bouabdallah R, Raffoux E, et al. Adult lymphoblastic lymphoma: a retrospective analysis of 92 patients under 61 years included in the LNH87/93 trials. *Leukemia* 2003;**17**:2220–4.
27. Micheli A, Mariotto A, Giorgi Rossi A, Gatta G, Muti P. The prognostic role of gender in survival of adult cancer patients. *Eur J Cancer* 1998;**34**:2271–8.
28. van Spronsen DJ, Janssen-Heijnen ML, Lemmens VE, Peters JW, Coebergh JW. Independent prognostic effect of co-morbidity in lymphoma patients: results of the population-based Eindhoven Cancer Registry. *Eur J Cancer* 2005;**41**(7):1051–7.
29. Battaglioli T, Gorini G, Costantini AS, Crosignani P, Miligi L, Nanni O, et al. Cigarette smoking and alcohol consumption as determinants of survival in non-Hodgkin's lymphoma: a population-based study. *Ann Oncol* 2006;**17**:1283–9.
30. Robotin MC, Law MG, Milliken S, Goldstein D, Garsia RJ, Dolan GM, et al. Clinical features and predictors of survival of AIDS-related non-Hodgkin's lymphoma in a population-based case series in Sydney, Australia. *HIV Med* 2004;**5**:377–84.
31. Diamond C, Taylor TH, Im T, Anton-Culver H. Presentation and outcomes of systemic non-Hodgkin's lymphoma: a comparison between patients with acquired immunodeficiency syndrome (AIDS) treated with highly active antiretroviral therapy and patients without AIDS. *Leuk Lymphoma* 2006;**47**:1822–9.
32. Cronin-Fenton DP, Sharp L, Deady S, Comber H. Treatment and survival for non-Hodgkin's lymphoma: influence of histological subtype, age, and other factors in a population-based study (1999–2001). *Eur J Cancer* 2006;**42**:2786–93.
33. Evans LS, Hancock BW. Non-Hodgkin lymphoma. *Lancet* 2003;**362**:139–46.