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## Original Paper

# The Rise in Incidence of Lymphomas in Europe 1985–1992

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**A collaborative study was carried out of the descriptive epidemiology of the lymphomas from seven countries across Europe in the period 1985–1992. Careful attention was paid to sources of information and the data quality in close collaboration with expert histopathologists. The data were classified as non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). An attempt was made to put the data into a modified version of the Revised European American Lymphoma (REAL) classification. We observed an overall rise in total NHL throughout the time period in all European countries but no such trend in HD. The increase in NHL overall being 4.2% per annum, representing an increase of 4.8% in males and 3.4% in females per annum, was only marked in middle and old age. Such increases were observed in all participating areas except in Burgundy. Different countries, however, have different base rates, the rates being highest in Scandinavia and the Netherlands. The analysis by subcategory classification suggested that the increase in NHL was confined to the follicle centre cell type, extra-nodal B-cell, nodal T-cell and nodal lymphomas not otherwise specified, categories. These new observations present a picture of real increase in case incidence with no obvious explanation. The increases in NHL do not appear to be due solely to better diagnoses. Pending other explanations or refutation, these present a compelling picture of an inexorable rise in incidence of this disease.** © **1999 Elsevier Science Ltd. All rights reserved.**

**Key words: lymphomas, NHL, HD, secular trend, incidence, Europe**
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## INTRODUCTION

REPORTS FROM several countries have expressed concern over the apparent rise in incidence of non-Hodgkin's lymphoma (NHL) [1–4]. Although this rise has been noted in earlier reports [5–7], it was believed that such results could be attributed to diagnostic artefact because of the known difficulties in making accurate diagnoses of the lymphomas. Some specialised lymphoma panels have reported very large inter-observer discrepancies in the Kiel and Rappaport diagnoses based on light microscopy [8]. However, better classification could also lead to the diagnosis of more cases, especially undifferentiated carcinoma, and hence an artificial increase in rates. In addition, considerable interobserver discrepancies have been eliminated in more recent times with the introduction of diagnostic aids. Counter to that view was the one suggesting that in developed countries diagnostic capabilities might have peaked in recent years and the rates should thus have reached a plateau by the mid-1990s.

Given the diversity of tumours within the NHL group, it would be expected that changes in incidence would be due to

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diagnostic artefact for some specific subtypes. However, identification of such changes requires a classification which is relevant to pathogenesis rather than simply clinical outcome. The publication of the Revised European American Lymphoma (REAL) classification [9] produced definitions of clinicopathological entities which correlate closely with cytogenetic and other factors likely to be important in pathogenesis.

In this study, a simplified classification was devised that included the main pathogenically dataset subtypes of lymphoma, whilst at the same time being compatible with previously acquired data. It was set up in selected countries across Europe from areas with a longstanding interest in lymphomas. The main aims were to investigate more recently acquired registry data, to review that data critically to achieve as high a standard of completeness and quality as possible, to convert the data into an imputed form of the REAL classification and to contrast that with rediagnosed case pathology. The purpose of the study was to determine if recent NHL data still show increases and if these increases in incidence are different throughout Europe. Finally, if changes in the incidence are observed, it is appropriate to examine changes by subtype.

This paper relates to the registry part of the study and how it might be possible for registry-based data to assist in answering these questions. Because part of the misclassification argument relates to the diagnostic reassignment of Hodgkin's disease (HD) cases to NHL, HD rates were also analysed in this study.

## PATIENTS AND METHODS

This is a study of new cases of NHL and HD from specific years within a series of well defined population bases. These are Odense, Denmark (population 2.7 million), Kuopio, Finland (population 1.0 million), Dijon, France (population 0.5 million), Florence, Italy (population 1.2 million), Ragusa, Italy (population 0.3 million), Eindhoven, the Netherlands (population 0.9 million), Tarragona, Spain, (population 0.5 million), Leeds, U.K. (population 3.5 million), making a total population under surveillance for this study of 10.6 million persons.

The following centres collected lymphoma cases through specialist registers, all of which had been in operation for some years prior to the commencement of this study; the LYFO registry in Denmark which commenced in 1983 and covers all lymphoma cases from Western Denmark; the haemopoietic malignancy register of Côte d'Or in Burgundy which started in 1980; and the Data Collection Survey of parts of the U.K. which has covered such a data collection in Yorkshire since 1984.

The other centres relied on their local cancer registries. In Finland (since 1952), Florence (since 1984), Ragusa (since 1981), the Netherlands (since 1955) and Tarragona (since 1980), cases are found from multiple overlapping data sources including histopathology records. All cancer registrations classify lymphomas by ICD 9 or an equivalent, except for Finland which uses ICD 7. The specialist registries use a subclassification system based on the Kiel [10] system which allows for flexibility in case allocation. In addition, there are cancer registries collecting, independently, data on lymphomas in Denmark and the U.K. Further details of some of the cancer registries are to be found in *Cancer Incidence in Five Continents* [6, 11] and Coebergh and associates [3].

In some instances, therefore, cross-checks were possible between specialist registers and cancer registries and this was done to ensure maximum coverage of cases. In other countries additional efforts were made to ensure the completeness of data for the purposes of the study for the principle years of study (1985–1992).

In order to avoid biases in the data over time, which could result from improved diagnostic approaches such as flow cytometry, the data were grouped into all NHL, all HD and seven subcategories of NHL which roughly correspond to subtypes recognised by the REAL classification. The aggregated categories used were accumulated from ICD-0 and the details are available from the corresponding author on request. They are non-Hodgkin's lymphoma (all types and all sites, pooled), Hodgkin's disease (all types, pooled), nodal diffuse large B-cell disease, nodal follicular centre cell, nodal mantle cell and nodal disease not otherwise specified. In addition, there are a nodal T-cell group and two extranodal categories of T and B cell, respectively. We specifically excluded the categories of small lymphocytic lymphoma/chronic lymphocytic leukaemia, as there is known to be a significant pool of subclinical disease in the population. The same is true of myeloma and plasmacytoma, which were similarly excluded from the analyses. Finally, lymphoblastic disease was so rare in adults that it was excluded from analyses by subtype in the report. No children were included in this study because earlier reports from childhood tumour registries consistently failed to find any indication of increases in incidence of NHL.

In each country the epidemiologists worked closely with histopathologists to convert the data in their registries into a form of the REAL classification. This proved possible in all countries except Finland, for which only aggregated data were available. This is because the Finnish registrational system utilises ICD-7 only. With that exception, these categories have been amassed from the registries using both ICD-classifications of type and site and ICD-0 aggregations (ICD-0 1990). The group 'Non-Hodgkin's lymphoma' is an amalgamation of all lymphoma categories except HD.

The registries' data had not been classified according to REAL because the bulk of the registrations predated the classification. However, common ground existed between registries in the use of ICD site codes enabling extranodal lymphomas to be identified and the use of Kiel or related classifications enabled the majority of registries to assign their lymphomas into the created REAL categories.

Each country was able to provide population data from relevant censuses or ongoing population counts appropriate to the period of case collection. The results presented in this paper comprise age- and sex-specific incidence rates for the population of cases aged 15–79 years. These were calculated by dividing the number of cases in each age group by the respective person years estimate, and multiplying this by 100 000. The directly standardised incidence rate was computed by applying the observed rates by age and sex to a reference population whose age and sex distribution is fixed in advance.

In addition, temporal variations were expressed as an annual percentage change in the incidence rates. These annual percentage changes were obtained from fitting a Poisson regression model, which also gave a test of significance for the temporal trend. Further details of these methods can be found in Cartwright and associates [12].

*Table* 1. *Malignant lymphoma: total case numbers collected in each region* (1985–1992) *and used in the analysis (ages* 15–79 *years)*

| | Male | Female | Total |
|---|---|---|---|
| Non-Hodgkin's lymphoma (NHL) | | | |
| Denmark | 1236 | 1013 | 2249 |
| Finland | 388 | 372 | 760 |
| France* | 138 | 104 | 242 |
| Italy: Florence† | 462 | 397 | 859 |
| Italy: Ragusa | 65 | 42 | 107 |
| The Netherlands | 366 | 242 | 608 |
| Spain | 124 | 116 | 240 |
| U.K. | 1208 | 941 | 2149 |
| Total | 3987 | 3227 | 7214 |
| Hodgkin's disease (HD) | | | |
| Denmark | 317 | 192 | 509 |
| Finland | 83 | 64 | 147 |
| France* | 46 | 32 | 78 |
| Italy: Florence† | 166 | 146 | 312 |
| Italy: Ragusa | 25 | 26 | 51 |
| The Netherlands | 85 | 57 | 142 |
| Spain | 53 | 22 | 75 |
| U.K. | 359 | 263 | 622 |
| Total | 1134 | 802 | 1936 |
| Total lymphomas | 5121 | 4029 | 9150 |

*Years 1986–1992; †years 1985–1991.

*Table* 2. *Uniform standardised incidence rates (x per* 100 000 *per year) by country for non-Hodgkin's lymphoma (NHL) (all types, all sites) and Hodgkin's disease (HD) for* 1985–1992 *(ages* 15–79 *years)*

| | NHL | | | HD | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| Denmark | 19.5 | 14.5 | 16.8 | 3.6 | 2.1 | 2.9 |
| Finland | 20.9 | 15.8 | 18.0 | 3.1 | 2.4 | 2.8 |
| France | 16.2 | 10.7 | 13.2 | 4.0 | 2.4 | 3.1 |
| Italy: Florence | 17.2 | 12.6 | 14.7 | 5.4 | 4.2 | 4.7 |
| Italy: Ragusa | 9.6 | 5.4 | 7.4 | 2.9 | 2.8 | 2.8 |
| The Netherlands | 21.8 | 12.2 | 16.4 | 2.9 | 1.8 | 2.3 |
| Spain | 10.4 | 8.7 | 9.5 | 3.1 | 1.4 | 2.3 |
| U.K. | 15.0 | 9.8 | 12.2 | 3.2 | 2.2 | 2.3 |

## RESULTS

It was possible to collect data for all countries for the period 1985–1992 except for France (1986–1992) and Italy (Florence, 1985–1991).

There were a total of 9150 cases, the majority originating from Denmark, Italy (Florence) and the U.K. (Table 1).

When NHL (all sites, all types) and HD were examined, the magnitude of the overall standardised rates (per 100 000 per year) for each country were somewhat different (Table 2). The range of HD varied 2-fold, from 2.3 (Spain, The Netherlands and the U.K.) to 4.7 (Italy, Florence), whilst a wider range of variation was seen in NHL, from a low of 7.4 (Italy, Ragusa) to a high of 18.0 (Finland), when the pooled sexes were examined.

Each study area was investigated for changes in time and also the data from all registries were pooled to give an overall European rate of change. These results are shown in Table 3. Assuming that the trends are all linear in nature, they are expressed as a percentage annual change. For all countries pooled, there was a significant increase in NHL of 4.8% in males and 3.4% in females. There was some variation between countries (Figure 1). Increases in females were usually less than males. Table 4 shows that the increase in NHL incidence was present in men for all age groups, but only in women aged 45 years and over.

The accumulated case numbers for all registries were pooled for all countries by year for all HD and NHL cases and showed the analysis in toto comprised 1936 and 6454 cases, respectively. In addition, the total case numbers by imputed subtype were calculated for all countries pooled (apart from Finland). There were found to be 1334 cases of diffuse large B cell, 1251 cases of follicle centre cell, 373 cases of mantle cell, 1563 cases of nodal disease NOS, 131 cases of nodal T cell, 158 cases of extranodal T cell, and 1644 cases of extranodal B cell. Figure 2 shows the proportions by subtype by country. This indicates that, for example, overall extranodal disease is roughly 30% in each country.

Table 5 shows the trends in terms of the assumed linear change with percentage annual increases (decreases) and 95% confidence intervals. There were moderate increases in follicle centre cell, nodal lymphomas and extranodal B cell, and a dramatic increase in nodal T cell disease.

## DISCUSSION

This study is unique in several respects. It is the first time registries of different degrees of basic specialisation and

*Table* 3. *Estimates of yearly percentage changes in incidence rates (*15–79 *year olds) with associated* 95% *confidence intervals*

| | Male | Female | Pooled |
|---|---|---|---|
| Non-Hodgkin's lymphoma | | | |
| Denmark | 2.9 (0.4–5.4) | 2.4 (− 0.3–5.2) | 2.7 (0.8–4.5) |
| Finland | 6.8 (2.2–11.6) | 2.1 (− 2.4–6.7) | 4.5 (1.3–7.8) |
| France | 3.4 (− 4.9–12.4) | 2.0 (− 7.3–12.3) | 2.8 (− 3.5–9.5) |
| Italy: Florence | 6.5 (1.7–11.5) | 7.3 (2.1–12.7) | 6.9 (3.3–10.5) |
| Italy: Ragusa | 7.7 (− 3.3–20.0) | 8.6 (− 5.1–24.2) | 8.0 (− 0.7–17.5) |
| The Netherlands | 7.5 (2.7–12.4) | 3.0 (− 2.5–8.8) | 5.7 (2.1–9.4) |
| Spain | 6.8 (− 1.2–15.4) | 9.4 (0.9–18.6) | 8.0 (2.2–14.3) |
| U.K. | 4.0 (1.5–6.6) | 2.7 (− 0.2–5.6) | 3.5 (1.6–5.4) |
| All countries | 4.8 (3.4–6.2) | 3.4 (1.8–5.0) | 4.2 (3.1–5.3) |
| Hodgkin's disease | | | |
| All countries | − 0.2 (− 2.7–2.5) | 0.4 (− 2.6–3.5) | 0.1 (− 1.9–2.1) |

These were obtained by fitting a Poisson regression model.

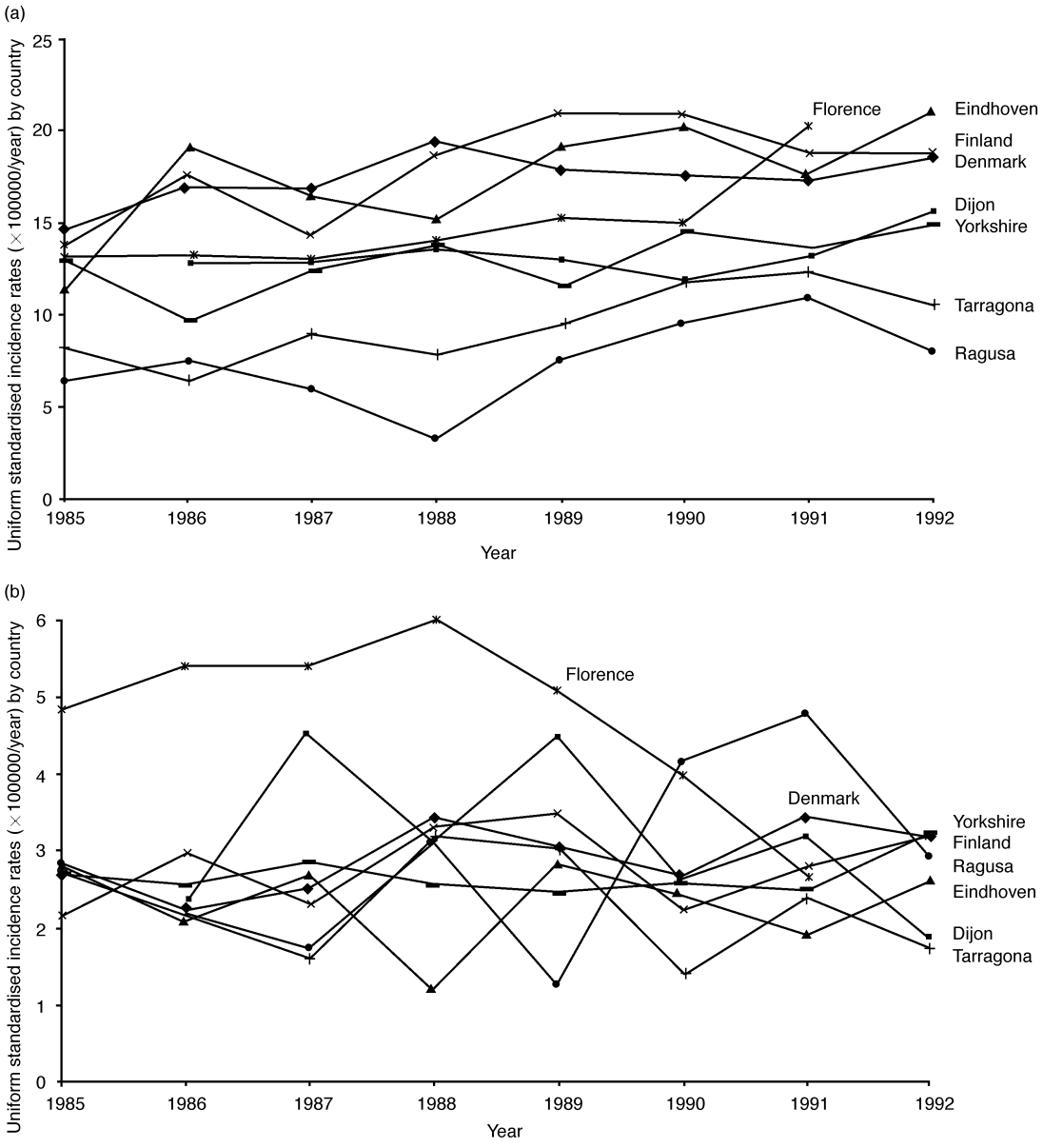


**Figure 1. Changes in the standardised incidence rates by country from 1985 to 1992 for (a) non-Hodgkin's lymphoma—all types, all sites; (b) Hodgkin's disease.**

*Table* 4. *Estimates of yearly percentage changes in incidence rates for three age bands with associated* 95% *confidence intervals*

| Age band (years) | | Estimate of annual % change | 95% Confidence intervals |
|---|---|---|---|
| 15–44 | Men | 3.6 | (0.2–7.0) |
| | Women | 0.7 | (− 3.4–4.9) |
| | Pooled | 2.4 | (− 0.2–5.1) |
| 45–69 | Men | 4.6 | (2.7–6.6) |
| | Women | 4.2 | (1.9–6.4) |
| | Pooled | 4.4 | (3.0–5.9) |
| 70–79 | Men | 5.9 | (3.2–8.6) |
| | Women | 3.4 | (0.8–6.1) |
| | Pooled | 4.7 | (2.8–6.6) |

These were obtained by fitting a Poisson regression model for total NHL.

sophistication have been very thoroughly perused and modified in attempts to achieve a uniform registrational standard for the lymphomas. It is also the first occasion when an attempt has been made to reconstruct such data to the REAL classification, which is likely to be relevant to pathogenesis. This work is the product of careful collaboration between epidemiologists and haematopathologists. Although some of the findings confirm expected trends in disease incidence, this study has also produced unique and unexpected findings. These include the relative similarities of the rates of increase of NHL across countries with diverse cultures, the wide range of "base" rates between countries and the apparent confinement of these rises to certain subtypes of NHL. This is also despite the wide variation in the case numbers contributing to the study in which two countries (the U.K. and Denmark) contributed over half the cases.

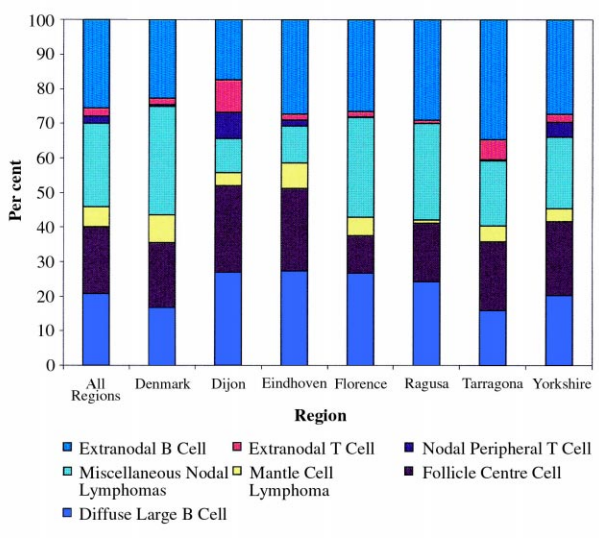


**Figure 2. Proportions of non-Hodgkin's lymphoma subtypes by region.**

We have confidence in the assignment of cases into the broad categories of NHL (all types, all sites) and HD due to the careful reassessment of the original data. Further, there are good reasons to support the veracity of the results despite their variations in base rates from country to country. These rate differences are, most likely, real and not a consequence of the registrational procedures. Each registry collects information from multiple overlapping sources, and does not incorporate cases with inadequate information, most of the pathology laboratories had incorporated the use of cell surface markers and related modern technology into their diagnostic armamentarium. Further, the two registries able to cross-check with other sources (the U.K. and Denmark) have incorporated all available case data from all sources and yet have quite different rates.

The weakest part of the study must be the assignment of registrational NHL categories into the REAL subtypes as used in this paper. Nevertheless, all registries can distinguish most nodal and extranodal registrations with confidence and the use of markers makes assignment to T or B cell types more certain. Further, the internal consistency of the results between countries within categories is encouraging.

In all registries, an increase in incidence of NHL was observed consistent with that seen elsewhere from both routinely collected data sets [3, 7, 13] and from specialist registries [1, 2, 5, 14]. These increases were not, in these data, accounted for by corresponding decreases in HD diagnoses. In fact the data show no clear pattern in secular trends in HD. Internationally HD trends are complex and conflicting in that some populations demonstrate clear increases in incidence whilst many do not [7]. In certain populations, the younger female rates are increasing [15, 16]. Where increases occur, they are largely in the 44–79 year age group but not specifically in the older groups—males aged 15–44 years also have a significant rate of increase. All this argues against a purely diagnostic artefact.

The reason for this overall increase in NHL has been the subject of much speculation [17], but little resolution. It is clear that the major risk factors associated with NHL are all linked to aspects of chronic immunosuppression or chronic antigenic stimulation in the individual, either from inherited risks, acquired disease, infection, or environmental exposure. Risks of 10-fold or more are associated with those treated with immunosuppressive drugs [18], diseases such as glomerulonephritis or rheumatoid arthritis [19] and HIV infection [20]. Almost all other investigated associations result in risks of 2-fold or less, these include exposure to agrichemicals [21], petrochemicals [22], nitrate levels in drinking water [23], hair dye use [24] or blood transfusions [25].

Some of these risks must play a part in recent increases; HIV and Hepatitis C Virus (HCV) infections and the increase in number of transplantations, for example. However, these risk factors do not explain a trend which started over 30 years ago and which is of such a high magnitude in so many different countries. This has led to speculation as to other very common exposures which result in NHL as a long-term risk. These include antibiotic usage, active pollutants from the internal combustion engine and sunlight exposure [26, 27].

The lower rate of increase in women compared with men is unlikely to be simply due to collection bias and may mean risks vary between the sexes. No increases are seen in children, nor consistently under the age of 30 years [28] and the data presented here are broadly consistent with that observation but also suggest very similar rates of increase for the whole 45–79 year age group.

Further insights might be gained from examination of the subtypes of NHL. This paper shows, for the first time, marked differences between the subtypes with the rises apparently confined to the following groups: follicle centre cell and extranodal B-cell types, nodal T cell and the group of nodal lymphomas NOS. This latter group includes several rare entities, such as hairy cell leukaemia, but the bulk comprises cases not definitively classified by the registries. To some extent this group, dominated by registry-based cases with inadequate diagnostic information, would be expected to remain constant or to dwindle with the improvements in diagnosis. Careful perusal of the data shows that the increase

*Table 5. Estimates of yearly percentage changes in incidence rates with associated 95% confidence intervals*

| Subtype | Male | Female | Pooled |
|---|---|---|---|
| Diffuse large B-cell | 0.0 (− 3.1–3.2) | 3.0 (− 0.6–6.8) | 1.3 (− 1.0–3.8) |
| Follicle centre cell | 3.8 (0.2–7.4) | 5.4 (1.8–9.2) | 4.6 (2.1–7.2) |
| Mantle cell | − 1.7 (− 7.2–4.1) | − 5.6 (− 12.2–1.4) | − 3.2 (− 7.5–1.3) |
| Nodal lymphoma NOS | 7.1 (4.0–10.3) | 4.4 (1.0–8.0) | 6.0 (3.7–8.4) |
| Nodal T-cell | 18.3 (7.8–29.8) | 17.1 (1.0–35.6) | 18.0 (9.1–27.7) |
| Extranodal T-cell | 3.0 (− 5.2–11.9) | − 11.1 (− 21.5–0.8) | − 1.5 (− 8.1–5.5) |
| Extranodal B-cell | 6.4 (3.4–9.6) | 3.4 (0.2–6.7) | 5.0 (2.8–7.3) |

These were obtained from fitting a Poisson regression model and are given by subtypes using pooled data from all countries.

is largely due to changes in the Danish registry, most other countries showing no obvious trend. The reason for this is not clear. One possible explanation could be the increasing use of minimal sampling techniques such as fine needle aspiration in elderly patients who are not candidates for intensive treatment. The numbers of nodal NOS are quite small for certain countries but substantial for others representing, on average, 23% of all registrations. The registries with the fewest number of NOS categories are from Dijon and Eindhoven (c. 10%) whilst the most are from Denmark, Florence and Ragusa (c. 30%) and the other countries are intermediate. The fact that this group of nodal NOS types is increasing would reflect classification schemes in different areas and also the possibility that changes in classification, pending the introduction of the REAL classification, were starting to occur, which resulted in difficulty in assigning cases to the Kiel classification and hence the increasing assignment to an 'NOS' category. This aspect will be thoroughly addressed in the pathology review.

The increase in follicle centre lymphoma is mainly a feature of Tarragon, Dijon and Florence, in the latter area the rate increased 6-fold but at the end of the study period approximated to the overall average for this category. It is, therefore, possible that this reflects changes in diagnosis rather than time-related increases. The changes in nodal T cell disease are due to very small numbers and are unreliable.

The main finding is the change in extranodal B-cell lymphoma. This observation awaits confirmation. Central nervous system lymphomas have been increasing in southeast England [29], partly due to improved diagnostics and more recently, but only in some of the countries, HIV infections. Other extranodal NHL increases have not been reported from most epidemiological studies [3].

In conclusion, these results provide further and considerable evidence for the increasing incidence of NHL in Europe. The rates of increase are broadly consistent throughout Europe within an overall range between 2.7 and 8% with a mean of 4.2% per year rise in 15–79 year olds. Common or shared environmental exposures seem the likely explanation. The confinement of this increase to specific age groups and subtypes needs confirmation from other sources. However, this study shows no sign that the increases abated in the more recent years of study and provides the impetus to investigate further the underlying causes of an epidemic which may have profound consequences over future years in terms of public health.


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