Attenuation of the epidemic increase in non-Hodgkin’s lymphomas in Spain

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Background: Attenuation of the epidemic increase in non-Hodgkin’s lymphoma (NHL) incidence has recently been reported in the USA and Nordic European countries. After two decades of steadily increasing NHL, this study sought to ascertain whether a similar stabilisation might have taken place in Spain in recent years.

Patients and methods: NHL cases were drawn from 13 population-based Spanish cancer registries with a record of at least 10 years of uninterrupted registration during the period 1975–2004. Overall and age-specific changes in incidence rates were evaluated using change-point Poisson models, which allow for accurate detection and estimation of trend changes.

Results: A total of 21 335 NHL cases (11 531 male and 9804 female) were identified. Although overall age- and registry-adjusted incidence rates rose by 5.74% annually among men and 6.58% among women across the period 1975–95, a statistically significant change-point was nevertheless detected in both sexes in 1996, followed by stabilisation.

Conclusions: In Spain, NHL incidence levelled off in 1996 after a sharp increase during the 1970s and 1980s. This stabilisation is, partially at least, linked to the decrease in incidence of AIDS-related lymphomas among young adults.

Key words: change-point transition models, incidence trends, non-Hodgkin’s lymphoma, population-based study, Spain

Introduction

Non-Hodgkin’s lymphomas (NHLs) are a heterogeneous group of diseases with different types of behaviour, prognosis and epidemiology. While a few risk factors for selected types of NHL have been identified, including conditions linked to the immune system [1, 2], immunodeficiency virus, HIV and hepatitis C virus [3–5], and occupational and environmental exposure [6, 7], the causes of most NHLs remain largely unknown [8].

In Spain (1998–2002), NHL is the eighth leading tumour in men and the fifth in women (3.0% of all male and 4.0% of all female cancers) [9]. Over the past 30 years, incidence of this disease has increased, particularly in industrialised countries [10–14]. While improved cancer reporting, changes in lymphoma classification and increase in AIDS-associated lymphomas have contributed to the striking escalation of disease incidence, these factors are estimated to account for only ~50% of the increase in observed incidence [15].

Recently, an attenuation of the epidemic increase in NHL incidence has been reported in some developed countries [16, 17]. To ascertain whether a similar pattern might have taken place in Spain in recent years, this study analysed changes in NHL incidence in Spain over the period 1975–2004. In view of differences in the impact of the HIV epidemic on age-specific incidence rates, trends were also analysed separately for men and women aged 0–24, 25–39, 40–54, 55–69 and ≥70 years.

Methods

data source

The number of NHLs, broken down by 5-year age group (0–4, 5–9, …, 80–84 and ≥85 years) and single year of diagnosis, was provided by 13 population-based cancer registries (Asturias, Navarre, Basque Country, La Rioja, Girona, Tarragona, Zaragoza, Albacete, Cuenca, Murcia, Granada, Mallorca and Canary Islands) which are members of the European Network of Cancer Registries and had been collecting data for at least 10 consecutive years during the designated study period (1975–2004), with data collection.
periods ranging from 1975–79 to 2000–04. NHL corresponded to codes C82–85 and C96 of the 10th revision of the International Classification of Diseases. Overall, the 13 registries included in this study cover ~26% of the total Spanish population (10 109 596 persons covered in 2001), and serve 17 different Spanish provinces located mainly in the east of the country, along a band running from the northern Cantabrian coast to the southern Mediterranean area. Estimates of the mid-year populations covered by these registries during the study period were obtained from the Spanish National and Regional Institutes of Statistics.

statistical analysis
Age-standardised incidence rates (ASIRs) of NHL were calculated for each registry, sex and 5-year period (1975–79, 1980–84, 1985–89, 1990–94, 1995–99 and 2000–04) using the direct method with the European standard population taken as reference. Assuming a Poisson distribution for the number of cases broken down by registry, sex, 5-year period and age group, the ratio of age-adjusted incidence rates and its 95% confidence interval (CI) were computed for each individual registry with respect to all the registries combined, for each sex and 5-year period.

Changes in age- and registry-adjusted incidence rates over the study period were evaluated separately for men and women using transition change-point models, again assuming a Poisson distribution for the number of cases in each stratum. These transition change-point models are similar to the widespread joinpoint regression [19], but, instead of assuming an overall trend made up of intersecting linear segments with an implausible sharp bend at the change-point, the proposed model allows for more gradual transitions between the linear trends. The transition change-point model provides an asymptotic test for the existence of a change-point, the estimate and 95% CI for the location of the change-point, and the estimates and 95% CIs for the annual percentage changes (APCs) in incidence rates below and above the estimated change-point. All statistical tests were two-sided, and $P$ values <0.05 were deemed statistically significant. Further methodological details and epidemiological applications of the proposed change-point model are provided elsewhere [20, 21].

The above-described models were also used to evaluate specifically the trend in NHL incidence among men and women aged 0–24, 25–39, 40–54, 55–69 and ≥70 years.

results
A total of 21 335 incident cases (11 531 male and 9804 female) of NHL were identified in the 195 302 907 person-years covered by the 13 Spanish registries from 1975 to 2004. Overall, the ASIR increased steeply in both sexes from 3.9 cases per 100 000 person-years in 1975–79 to 12.0 cases per 100 000 person-years in 2000–04. The rate ratio between the Canary Islands and La Rioja was 2.45, indicating marked geographical differences in the incidence of this type of cancer.

Among men, the ASIR increased from 4.9 cases per 100 000 man-years in 1975–79 to 14.2 in 2000–04; and among women, the ASIR increased from 3.0 cases per 100 000 woman-years in 1975–79 to 10.1 in 2000–04. There was a substantial excess incidence of NHL among males (generally ~40%) which remained constant across the study period (Table 1).

Figure 1 depicts age- and registry-adjusted incidence rates of NHL by single year of diagnosis in all Spanish registries, along with the estimated time trend obtained from fitting a change-point model for all ages (A1 for men and B1 for women) and for age groups (A2 for men and B2 for women).

Table 2 shows trend analyses for all ages and for individual age groups. During the period 1975–2004, there was a significant annual increase in the all-age incidence rate of 3.50% in men and 3.85% in women. Although incidence of NHL increased steadily during the 1980s and 1990s, it tended to stabilise in recent years. The change-point model confirmed this result, with a gradual but statistically significant change in trend observed among men in 1996 (95% CI 1994–1998; $P$ value for the existence of a change-point <0.001) and among women in 1995 (95% CI 1992–1999; $P$ value for the existence of a change-point <0.001). While the NHL rate increased among men by 5.74% (95% CI 5.10% to 6.39%) per annum until 1996, followed by a gradual stabilisation thereafter (APC of –0.11%; 95% CI –0.99% to 0.78%) (Figure 1 A.1), it increased among women by 6.58% (95% CI 5.79% to 7.37%) per annum until 1995 and was likewise followed by a gradual stabilisation thereafter (APC of 0.33%; 95% CI –0.57% to 1.26%) (Figure 1, B.1).

We next analysed NHL incidence trends by age group. There was no evidence of a change in trend among children and young adults aged 0–24 years. Although the incidence of NHL rose steeply among men and women aged 25–39 years from 1975 to the mid-1990s, it tended to decline in recent years. Among men, a significant and sharp downturn was detected in 1995, with incidence increasing by 10.82% per annum until 1995 and declining by –4.74% per annum thereafter. Among women, however, the downturn was detected later, i.e. in 1999, with the NHL rate increasing by 6.97% per annum until 1999 and declining by –3.92% per annum thereafter. Among men aged 40–54 years there was a significant and gradual levelling off in 1999, with an annual increase in incidence of 5.54% below this threshold, followed by a gradual stabilisation. Among women aged 40–54 years, incidence increased by 9.19% annually until 1990, followed by a gradual stabilisation.

In men and women aged 55–69 years incidence increased by 6.94% and 5.92%, respectively, until 1992, followed by a gradual stabilisation in both sexes. Lastly, among men and women aged ≥70 years, there was a significant and gradual levelling off in 1994, followed by a gradual stabilisation (Figure 1 A2 and B2).

discussion
This study describes the changing incidence trends in NHL in Spain over the last three decades, as assessed by transition change-point models. The increased incidence of NHL reported in Spain during the 30-year study period coincides with that described for other geographical areas [10, 12, 14, 22]. To understand changes in NHL incidence, it is important to consider precisely which factors might be influencing observed trends in Spain. These include: (i) incompleteness of case registration due to lack of participation or poor reporting practices by participating hospitals, particularly in the early period; (ii) changes in the definition of NHL, which meant that, in certain subtypes of NHL, cases were recruited from what were previously defined as benign lymphoid disorders, e.g. in the updated classification, angioimmunoblastic lymphadenopathy is now deemed to be a peripheral T-cell lymphoma. Moreover, a variant of lymphoma that is found in extranodal mucosa tissue...
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<tr>
<td></td>
<td>Cases</td>
<td>Rate</td>
<td>RR$^a$</td>
<td>Cases</td>
<td>Rate</td>
<td>RR$^a$</td>
</tr>
<tr>
<td>Zaragoza</td>
<td>130</td>
<td>3.2</td>
<td>0.82</td>
<td>(0.73, 0.93)</td>
<td>148</td>
<td>3.4</td>
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<td>Navarre</td>
<td>123</td>
<td>5.1</td>
<td>1.31</td>
<td>(1.15, 1.49)</td>
<td>172</td>
<td>6.8</td>
</tr>
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<td>Tarragona</td>
<td>1978–2002</td>
<td>143</td>
<td>5.3</td>
<td>0.98</td>
<td>(0.85, 1.15)</td>
<td>178</td>
</tr>
<tr>
<td>Asturias</td>
<td>1982–2001</td>
<td>249</td>
<td>6.8</td>
<td>1.28</td>
<td>(1.15, 1.42)</td>
<td>488</td>
</tr>
<tr>
<td>Murcia</td>
<td>1983–2003</td>
<td>96</td>
<td>5.4</td>
<td>1.00</td>
<td>(0.83, 1.21)</td>
<td>331</td>
</tr>
<tr>
<td>Granada</td>
<td>1985–2004</td>
<td>222</td>
<td>5.8</td>
<td>0.83</td>
<td>(0.73, 0.94)</td>
<td>296</td>
</tr>
<tr>
<td>Basque Country</td>
<td>1986–2004</td>
<td>639</td>
<td>7.4</td>
<td>1.06</td>
<td>(1.00, 1.11)</td>
<td>1144</td>
</tr>
<tr>
<td>Mallorca</td>
<td>1988–2000</td>
<td>115</td>
<td>9.2</td>
<td>1.32</td>
<td>(1.10, 1.59)</td>
<td>279</td>
</tr>
<tr>
<td>Girona</td>
<td>1994–2004</td>
<td>80</td>
<td>13.9</td>
<td>1.47</td>
<td>(1.17, 1.84)</td>
<td>439</td>
</tr>
<tr>
<td>Albacete</td>
<td>1991–2002</td>
<td>127</td>
<td>8.5</td>
<td>0.89</td>
<td>(0.75, 0.97)</td>
<td>175</td>
</tr>
<tr>
<td>Canary Islands</td>
<td>1993–2004</td>
<td>324</td>
<td>13.6</td>
<td>1.44</td>
<td>(1.29, 1.60)</td>
<td>1075</td>
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<td>La Rioja</td>
<td>1993–2001</td>
<td>36</td>
<td>4.9</td>
<td>0.52</td>
<td>(0.37, 0.73)</td>
<td>121</td>
</tr>
<tr>
<td>Cuenca</td>
<td>1993–2004</td>
<td>30</td>
<td>5.4</td>
<td>0.57</td>
<td>(0.39, 0.85)</td>
<td>81</td>
</tr>
</tbody>
</table>

$^a$Age-adjusted rate ratio (95% CI) for each registry with respect to all registries combined in the corresponding 5-year period.
Figure 1. Age- and registry-adjusted incidence rates of non-Hodgkin's lymphoma over the period 1975–2004 among men (A1, all ages; and A2, by age group) and women (B1, all ages; and B2, by age group) at all Spanish registries. The observed rates (dotted line) were obtained by using nominal categories for each year of diagnosis, and the estimated time trend (solid line) and its 95% confidence interval (CI) (dashed line) were obtained from fitting a change-point model (see Methods section).
The results of this study are strengthened both by the inclusion of the latest available data from all population-based was falsely classed as a pseudolymphoma [23]; (iii) changes in tumour ascertainment, which accounts for the lower proportion of cases with pathological confirmation in the earlier period; (iv) an increase in the detection of NHL cases due to widespread advances in diagnostic technology (diagnostic imaging tools) [24]. Indeed, new immunological concepts and methods developed over the past three decades have revolutionised diagnostic criteria, classification and understanding of NHL; (v) changes in the prevalence of related diseases, such as AIDS, and in other risk factors. Relative risk of NHL is high in persons with AIDS, with risk estimates of 120 for males and 190 for females in the reported increase in NHL among young adult men. The AIDS epidemic decreased sharply in most risk groups after 1996. This decline was mainly attributed to the introduction of potent antiretroviral therapies [27] that delay onset of AIDS in the HIV-infected population [28] and lengthen survival among AIDS sufferers. Furthermore, due to the predominance of drug users among AIDS patients in Spain, changes in drug-use practices aimed at avoiding risk of HIV transmission could explain the marked fall-off in AIDS incidence in recent birth cohorts [29].

The decline in NHL rates among young adults has been described in the USA [17, 22], in Nordic countries [16] and, more recently, in Catalonia [30]. The US study reports a decrease in the incidence of NHL subtypes associated with AIDS. In Catalonia, the population-attributable fraction of HIV in the incidence of NHL decreased from 20% in the period 1988–89 to 6.8% in the period 1998–99 [25].

The explanation for the slowing in the rate of increase observed for adults aged >40 years during the 1990s is more elusive. Improvements in diagnostic methods, which may explain some of the increasing incidence observed among older persons in the 1970s and 1980s, are unlikely to be related to a slowing in the trend. The tendency towards stabilisation in incidence of NHL could reflect full implementation of modern diagnostic procedures or recent saturation of general population exposure to relevant risk factors. While the possibility of a stabilisation or saturation in the exposure level to relevant risk factors is an alternative explanation, the fact that the causes of NHL are largely unknown renders it difficult to speculate just which factors may have contributed to the observed levelling-off. Among environmental exposure, pesticides have been related to the incidence of NHL [31], and the regulation of or ban on the use of chlorophenols, certain phenoxy herbicides and some ‘persistent organic pollutants’ in Spain in the 1970s [32] could have contributed to the stabilisation of NHL incidence in Spain. In line with this model, NHL rates would be expected to remain at current levels.

Our results show that the steady increase in NHL incidence observed in Spain during the 1970s and 1990s has come to a halt in recent years and that the subsequent pattern of evolution differs according to age group. Examination of NHL incidence in Spain by age group reveals that NHL rates remained stable in children and young adults (ages 0–24 years), in contrast to the results of the European ACCIS study [26], which reported a weak increase in incidence of NHL among children and adolescents. Nevertheless, it is no easy task to quantify the contribution of improvements in registration to the reported increase in NHL in Europe, and the established major risk factors do not seem to affect incidence in these young age groups.

Incidence rates of NHL among young adults aged 25–39 years rose dramatically in the mid-1980s, followed by an abrupt downturn in the mid-1990s. As noted above, the striking increase in NHL in the mid-1980s coincided with the HIV epidemic. The stabilisation and subsequent decline in NHL rates in the 1990s observed among young adults is probably also explained, to a large extent, by AIDS incidence patterns. Groups at high risk of developing HIV/AIDS tend to be males in the 25- to 49-year age range, something that may go some way to explain part of the high incidence of NHL among young adult men. The AIDS epidemic decreased sharply in most risk groups after 1996. This decline was mainly attributed to the introduction of potent antiretroviral therapies [27] that delay onset of AIDS in the HIV-infected population [28] and lengthen survival among AIDS sufferers. Furthermore, due to the predominance of drug users among AIDS patients in Spain, changes in drug-use practices aimed at avoiding risk of HIV transmission could explain the marked fall-off in AIDS incidence in recent birth cohorts [29].

### Table 2. Trends in age-adjusted incidence rates of non-Hodgkin’s lymphoma among men and women at Spanish registries

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Sex</th>
<th>Change-point Year (95% CI)</th>
<th>APC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P value Overall Below change-point Above change-point</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>Male</td>
<td>&lt;0.001 1996 (1994–1998) 3.50 (1.5, 4.35) 5.74 (4.4, 6.93) 0.11 (-0.99, 0.78)</td>
<td></td>
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<tr>
<td></td>
<td>Female</td>
<td>&lt;0.001 1995 (1992–1999) 3.85 (1.4, 4.21) 6.58 (5.79, 7.37) 0.33 (-0.57, 1.26)</td>
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<tr>
<td>0–24</td>
<td>Male</td>
<td>1.0 1995 (1992–1999) 0.99 (-0.18, 2.18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.0 1995 (1992–1999) 0.86 (-0.38, 2.33)</td>
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<tr>
<td>25–39</td>
<td>Male</td>
<td>&lt;0.001 1995 (1994–1997) 3.82 (2.71, 4.93) 10.82 (8.52, 13.17) -4.74 (-7.08, –2.34)</td>
<td></td>
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<tr>
<td></td>
<td>Female</td>
<td>0.016 1999 (1994–2002) 4.85 (3.5, 6.20) 6.97 (5.07, 8.91) -3.92 (-9.14, –1.58)</td>
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<tr>
<td>40–54</td>
<td>Male</td>
<td>0.029 1999 (1991 —) 4.12 (3.0, 5.28) 3.54 (3.3, 5.77) -1.71 (-5.44, 2.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.013 1990 (1985–1998) 4.21 (3.25, 5.17) 9.19 (5.89, 12.60) 2.46 (1.07, 3.87)</td>
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<tr>
<td>55–69</td>
<td>Male</td>
<td>&lt;0.001 1992 (1987–1998) 3.21 (2.59, 3.84) 6.94 (5.23, 8.68) 0.67 (-0.52, 1.87)</td>
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<tr>
<td></td>
<td>Female</td>
<td>0.013 1992 (1987–1998) 3.48 (2.78, 4.18) 5.92 (4.26, 7.61) 1.77 (0.55, 3.01)</td>
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<tr>
<td>70+</td>
<td>Male</td>
<td>&lt;0.001 1994 (1988 —) 4.00 (3.2, 4.85) 7.35 (5.81, 8.90) 0.59 (-0.86, 2.07)</td>
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<tr>
<td></td>
<td>Female</td>
<td>&lt;0.001 1994 (1991–1998) 4.12 (3.51, 4.73) 8.48 (6.96, 10.02) 0.051 (-1.27, 1.40)</td>
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</table>

*The upper limit of the 95% confidence interval (CI) could not be estimated due to the low number of cases.*
Spanish cancer registries with a minimum of 10 years of uninterrupted registration, resulting in ~20 000 registered cases of NHL, and by the use of appropriate statistical methods to detect trend changes. Nevertheless, several limitations must be considered when it comes to interpreting our findings. The population covered by the registries is located mainly in the east of Spain, and thus the observed trend in NHL incidence might not be generalisable to the western and central parts of the country. Heterogeneity in data quality across registries may have adversely affected our results, particularly in the latter part of follow-up, in which the change in the previously rising trend was detected. During the 1998–2002 period, however, the percentage of histologically confirmed NHL cancer cases was high, ranging from 86% to 97%, whereas the percentage of those registered solely on the basis of death certificates ranged from 0.6% to 4.0% [9]. In addition, the fact that our study period ended in 2004 means that there is likely to be some residual reporting delay. Finally, a major limitation of these interpretations of NHL incidence trends involves disease heterogeneity. NHL comprises many histologically, and perhaps biologically, distinct lymphocyte malignancies [33–36], each with poorly understood but putatively different aetiologies [37], and it is therefore not unreasonable to infer that this and other epidemiological analyses treating NHL as a single entity may well conceal informative trends for particular subtypes [37, 38]. We analysed all NHL cases jointly so as to ensure continuity and comparability with previous studies of NHL incidence trends which reported steady increases over time.

To sum up, we describe a decline in NHL incidence rates in Spain which particularly affected the 25–39 age group. This trend is probably related to the HIV epidemic, in which exposure to and the effect of the same widespread risk factors first increased and then possibly decreased, a reason why NHL rates should be expected to continue declining in this age group in Spain. In the age strata above 40 years, however, there has been a marked attenuation of the epidemic increase in NHL in Spain. Insofar as interpretation of NHL trends is concerned, the tendency towards stabilisation in NHL incidence reflects full implementation of modern diagnostic procedures and/or a recent stabilisation or decrease in general population exposure to unknown, albeit relevant, risk factors. In line with this model, NHL rates would thus be expected to remain at their current level.

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**disclosures**

The authors have indicated no conflicts of interest.

**references**


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