Rising Incidence of Non-Hodgkin’s Lymphoma in Spain: Analysis of Period of Diagnosis and Cohort Effects

M. Pollán, G. López-Abente, C. Moreno, A. Vergara, N. Aragonés, M. Ruiz, E. Ardanaz, and P. Moreo

Cancer Epidemiology Unit, National Center for Epidemiology, Carlos III Institute of Health, Sinesio Delgado 6, 28029 Madrid, Spain [M. P., G. L.A., N. A., M. R.J.]; Cancer Registry of Navarre, Navarre Public Health Institute, Leyre 15, 31003 Pamplona, Spain [C. M., E. A.]; and Cancer Registry of Zaragoza, Zaragoza Provincial Health Authority, Ramón y Cajal 68, 50004 Zaragoza, Spain [A. V., P. M.]

Abstract

Incidence trends in non-Hodgkin’s lymphomas for the period 1973–1991 were studied using data from Spain’s Zaragoza and Navarre registries. The overall rate of increase was 5.8% per year. Age-period-cohort models were used, also including sex and registry as explanatory variables. In these models, the variable period was categorized according to the observed changes in diagnostic availability during the length of the study. Non-Hodgkin’s lymphomas increased with age, and rates were 31% lower in women. Incidence was almost 50% higher in Navarre, but differences in registry procedures might account for this discrepancy. The rise affects all adult age groups and seems to be the result of changes related not only to the period of diagnosis, mainly ascribable to improvements in diagnostic and coding practices, but also to the birth cohort. According to the model, the risk increased with on-coming generations at a rate of 1.5% per year. The AIDS epidemic in Spain is unable to explain this trend, although it may well exert a stronger influence in the future. Additional knowledge is required to understand the observed rise and to prevent the growing numbers of cases that are expected in years to come.

Introduction

Non-Hodgkin’s lymphomas (NHL) NHLs3 are a heterogeneous collection of lymphoproliferative malignancies (1) with different behaviors and responses to treatment, and according to ICD-9 (2), comprise lymphosarcoma, reticulosarcoma, Burkitt’s lymphoma (ICD-9 200), and other malignant neoplasms of lymphoid tissue (ICD-9 202), including mycosis fungoides. Reports of a rapid increase in the incidence of NHL have come from around the world (3–13). In Europe, incidence has been rising since the 1960s, and recent rates of increase have been in the range of 15–40% every 5 years, with this increment being more pronounced in the European Union and Nordic countries (3). Incidence has also increased in Asia and America (3). In the United States, incidence has more than doubled in recent decades (8–10). Part of this rise might be due to the progressive availability of medical tools that enhance the sensitivity and specificity of NHL diagnosis, particularly among the elderly, a group which indeed showed the greatest increase (6, 13). However, most authors feel that this could hardly explain the extent and rate of the observed increment (4, 5, 8, 9, 12, 14).

In Spain, NHL mortality rates rose steadily over the period 1952–1986, registering an overall annual increment of 5% in both sexes, with NHL ranking among the tumors showing the highest increase (15).

Three different time-related factors may contribute to any observed trend in incidence, i.e., age at diagnosis, period of diagnosis, and year of birth. Standardized rates reduce the confounding effect of any change in the age distribution, but no distinction is drawn between period and cohort effects. Age-cohort models thus simultaneously study variability in rates on the basis of these three variables, attempting to separate their respective contributions to the observed trend (16–21).

Two Spanish cancer registries have been providing information about incidence for just over 20 years. The Zaragoza Cancer Registry, set up in 1960, was the first population-based registry in Spain. Its catchment area is the Province of Zaragoza, situated in Northeast Spain, with a population of 832,855. The Navarre Cancer Registry, dating from 1970, presently covers a population of 517,344. Navarre also lies in the north of the country, adjacent to Zaragoza.

This report analyses trends in NHL incidence in Zaragoza and Navarre over the period 1973–1991 and examines the influence of age, period of diagnosis, and birth cohort on the pattern plotted by the specific rates.

Materials and Methods

NHL was defined for study purposes as any case falling within ICD-9 rubrics 200 and 202 (2). This decision was made after verifying that the use of ICD-O codes produced a loss of 14% of cases due to lack of histological data. All cases diagnosed in both provinces between 1973 and the last available year, i.e., 1990 in Zaragoza and 1991 in Navarre, were included.

The study period was split into four intervals: 1973–1977, 1978–1982, 1983–1987 for both areas, and 1988–1990 in Zaragoza and 1988–1991 in Navarre. Age-specific rates for each sex and age group (0–4, 5–9, 10–14, . . . , 80+) were computed for each registry. Midpoint population estimates were calculated from all available censuses and municipal registers for the study period, using a log-linear polynomial model (22).
Non-Hodgkin's Lymphomas in Navarre and Zaragoza, Spain

Adjusted rates using the standard European population. (b) Evaluated in the following basis: (a) constant rate of change; (b) changes associated with the period of diagnosis; (c) changes associated with the birth cohort; and (d) both period and cohort effects in the same model. Nested models were compared using the log-likelihood ratio test. To ascertain whether it was possible to assume the same kind of age, period, and cohort effects for both registries and sex, the statistical significance of the corresponding interaction terms was tested.

Models including the three time-related factors (age, period, and cohort) do not have a single specific solution, owing to the interrelation between these variables (identifiability problem). In practical terms, this means that it is not possible to quantify the slope of the linear component of each of the effects without imposing any additional condition. Different solutions have been proposed, based on statistical or biological criteria (20, 21). Our choice here was based on the assumption that the period effect is mainly related to diagnostic accessibility. We thus replaced the period of diagnosis with a variable reflecting the availability of new medical technologies (computed tomography scanners in the case in point) for the respective time intervals considered in each province. The first scanner was installed in 1978 in Navarre, and in the same year two scanners went into service in Zaragoza. However, additional equipment was only installed from 1984 in Navarre and 1985 in Zaragoza. Taking these data into account, we decided to create a new period variable, CTP, assigned a value of 0 during the first and second periods (1973–1982) and 1 thereafter (1983–1991).

As an alternative, bearing in mind that the sum of the period and cohort slopes, denominated net drift, is estimable without imposing any condition on the model (18–21), two extreme solutions are also presented that resulted from alternatively attributing net drift to the period and cohort effects, respectively (20). These twin assumptions serve to trace out a sort of confidence bound which would contain the true estimators.

Results

During the study period, a total of 740 NHLs were diagnosed in Zaragoza and 681 in Navarre. Apart from the second period in Zaragoza, where the percentage of histologically confirmed cases was 86%, this proportion was always in excess of 90%.

Shown in Table I are age-specific rates and adjusted rates per sex, registry, and period. There was an increase in the adjusted rates during the study period in both registries and sexes. This rise appeared to be more marked in Navarre, where rates also proved to be consistently higher. Rates fell in Zaragoza during the second 5-year period, probably associated with a changeover in the reporting system, which until 1979 had been passive and then became active. The average annual increment proved greater in women than in men (7% versus 3% in Zaragoza, and 6% versus 5% in Navarre). The rise affected almost all age groups and, with some exceptions, the steepest rise was observed between the second and the third periods.

In the modeling process, all of the considered variables (age, sex, registry, period of diagnosis, and birth cohort) proved to be statistically significant, and no residual overdispersion of rates was found (deviance, 125.8 with 120 degrees of freedom). Because the inclusion of both period and cohort effects entails the need to impose a new constraint, we opted to replace the period by the CTP variable. As it was mentioned before, CTP considered only two time intervals of diagnosis based on the availability of computed tomography during the study. The goodness-of-fit with CTP taken as the period variable is almost

To allow for differences in age distribution, overall rates were age-adjusted using the European population as standard. A more detailed analysis was run, by taking adult age groups with more than 15 diagnosed cases in each registry over the period as a whole. Log-linear Poisson models were fitted, with age, sex, registry, period of diagnosis, and birth cohort as explanatory variables. We tested for overdispersion of rates, by evaluating whether the deviance from a model with all variables and two-factor interactions exceeded its degrees of freedom by >30%.

The explanatory terms, age, sex, and registry, were sequentially introduced into the model; this order was dictated by our predetermined opinion as to their relative influence on rate variability (18, 19). The time-trend component was then evaluated in the following basis: (a) constant rate of change; (b) changes associated with the period of diagnosis; (c) changes associated with the birth cohort; and (d) both period and cohort effects in the same model. Nested models were compared using the log-likelihood ratio test. To ascertain whether it was possible to assume the same kind of age, period, and cohort effects for both registries and sex, the statistical significance of the corresponding interaction terms was tested.

Table I: Incidence of NHLs in Zaragoza and Navarre: Age-specific rate and adjusted rates per 1,000,000 person-years

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* Adjusted rates using the standard European population.
Discussion

An abrupt increment in NHL has been observed in Zaragoza and Navarre, with an average increase of 5% per year. The rise affects all adult age groups and seems to be the result of changes related not only to the period of diagnosis but also to the birth cohort. These adjoining provinces displayed a noticeable difference in the number of NHL diagnosed; rates in Navarre were almost 50% higher than those for Zaragoza. Current incidence in Zaragoza (6.3 per 100,000 in males and 5.6 in females) is still low as against other European countries (23), whereas Navarre (11.0 per 100,000 in males and 7.6 in females) occupies an intermediate position.

This study could not use the current classification systems to differentiate between the various histologies of NHL, which might impose a limitation on our understanding of NHL epidemiology (24). However, no single classification system was in use during the study period, and most of them proved of little use for epidemiological purposes (25). Moreover, the epidemiological implications of cell morphology is unclear in the case of NHL (26).

Twenty % of all NHL cases arise outside lymph nodes, and despite the fact that ICD coding rules require them to be assigned to rubrics 200 and 202, they have often been coded within the organ in which they arise (3). There were 13 cases of extranodal NHL in Zaragoza and 2 in Navarre that had been coded neither as 200 nor as 202. They were not included in our study, but we verified that their inclusion would not have substantially changed the results.

Male NHL mortality rates are very similar in Navarre and Zaragoza (standardized rates for the period 1978–1992 of 3.7 per 100,000), whereas for females, the rate is slightly higher in Navarre (2.7) than in Zaragoza (2.3) (27). Incidence in children for both provinces would appear to be more homogeneous, however (28). Although the two registries use similar active reporting systems at present, until 1979 Zaragoza had recruited cases in a passive manner from the regional oncological center, and the change in the reporting system, together with the inclusion of other hospitals that started to provide also oncological care, produced a fall in incidence rates for NHL and other sites (28). Moreover, data quality indices are slightly better in Navarre (29). This would seem to imply that the ascertainment of cases has been more thorough in Navarre, and that the percentage of more benign cases would be higher. We cannot confirm this hypothesis, yet the number of cases diagnosed by death certificate in Zaragoza (7% on average) versus Navarre (less than a 2%) supports the assertion.

Among the different solutions proposed to address the identifiability problem, one that is particularly appealing has been suggested by Osmond and Gardner (16) and Decarli and La Vecchia (17). The main advantage of this procedure, based only on statistical considerations, is its objectivity. However, it would not be suitable here, because it overweights cohort against period effects. All other solutions impose arbitrary constraints (20, 21). For this reason, some authors have emphasized the need to select the final model, taking external relevant information into account (21). Our solution sought to accomplish this goal. Although a degree of arbitrariness cannot be ruled out, we think it more realistic than other alternatives.

The increase in incidence was manifested in both registries in a similar manner. Part of the rise has been ascribed to a period effect, probably reflecting the influence of diagnostic tools and the state of knowledge surrounding the disease. In-

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**Fig. 1.** Incidence rate ratios for NHL per birth generation (cohort effect) and year of diagnosis (period effect) according to the proposed model (thick lines). The dashed lines correspond to two extreme alternative models that attribute the whole trend to either the cohort (larger lines) or to the period (shorter lines) effect.

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identical (deviance of 125.9), whereas 1 degree of freedom is saved (121 instead of with 120). This difference is explained by the fact that CTP imposes not one but two conditions on the model: (a) it makes period 1 = period 2; and (b) period 3 = period 4. One such condition would have sufficed for the purposes of solving the identifiability problem, yet we decided to retain both; this was consistent with the information provided.

The effect of age, sex, and registry yielded by the above-mentioned model was consistent with what is observed in Table 1. Incidence in adults rose with age as a power function. On average, incidence among women was 31% lower than that among men (relative risk, 0.69; 95% confidence interval, 0.61–0.78). Finally, as against Zaragoza, Navarre had a statistically significant risk excess of almost a 50% (relative risk, 1.47; 95% confidence interval, 1.30–1.65).

Cohort and period effects are drawn on a logarithmic scale in Fig. 1. The solid line corresponds to the proposed solution. The remaining lines correspond to the two extreme solutions that serve to trace out an area that includes other possible alternatives. Period-related changes were more pronounced and occurred under our proposed model as a leap between the second and third periods. This strong assumption is further supported by the model, which ascribed the maximum trend to the period effect. On the other hand, risk increased with oncoming birth cohorts. This increase was greater pre-1912, registered a temporary drop around 1917, and increased at a lower rate for subsequent generations. There is a peak for birth cohorts born around 1942, but before drawing any conclusion, it should be recalled that this part of the curve is only based on age groups younger than 50.
Indeed, it is on this assumption that our final model is based, with the number of computed tomography scanners taken as an indicator of the feasibility of diagnosis. Although the main diagnostic procedure for these diseases is histopathological examination, chest and abdominal computed tomography scans are usually part of the staging evaluation and can reveal silent NHL affecting internal nodes. In general, advanced medical technologies were mainly implemented in Spain during the 1980s (30), and the CTP variable could also therefore act as an indicator of differences in the Spanish medical system during the study period.

Our assumption is rather conservative because it divides the overall increase (5.8% per year; 95% CI, 4.7%–7.0%), over-weighting the period effect (4.3% per year) against the cohort effect (1.5% per year). Yet even under this premise, our model shows an increasing risk linked to year of birth. Accordingly, these data support the fact that the so-called NHL epidemic (31) is also present in Spain. No straightforward explanation can be found, inasmuch as the etiology of NHL remains unknown.

Increased risk of NHL has been observed among AIDS patients (32, 33), with an incidence close to 29% among patients who survived 3 months of anti-retroviral treatment (34). The first case of AIDS in Spain was detected in 1981, and the epidemic among drug-users, who account for two thirds of the total number of cases in adults, shows a strong cohort effect, mostly affecting generations born around 1960–1970 (35). In Navarre, only five of the cases included in this study had a diagnosis of AIDS. This information was not available in Zaragoza, where the first AIDS case was diagnosed in 1986. Hence, as has been acknowledged previously, the rise in prevalence of HIV infection had little impact on NHL incidence during past decades (4, 5, 8, 9), although its impact may yet be overwhelming in the future (36).

The EBV seems to play a crucial role in the etiology of NHL among persons with acquired or inherited immunosuppression, as well as in some other NHLs, particularly among older patients (37). This suggests that there could be a subclinical immune suppression, leading to chronic activation of the EBV. Such a hypothesis necessarily calls for evidence of immunosuppressive agents that had become widespread in recent decades (37).

Pesticides may be one such agent. Exposure to phenoxy- and to other types of pesticides has proved to be a risk factor for NHL (38). This exposure is widespread in the farming and general population, and use of such substances has risen sharply during past decades (39). Although an ecological analysis carried out by the authors using NHL mortality at a provincial level failed to link the geographical pattern with herbicide consumption, their contribution to the observed rise cannot be ruled out.

Farmers have shown an excess of risk in several (39, 40), although not in all (41), studies. Although exposed to pesticides, they could also be equally exposed to oncogenic viruses carried by farm animals and to chronic antigenic stimulation from different sources (42). Increased risk has been found among persons employed in agriculture; forestry; construction; the fishing, paper-and-wood and leather industries; among hair-dye users; benzene workers; chemists; petroleum refinery personnel; anesthesiologists; and pathologists (42–44). Nevertheless, the proportion of NHL that can be attributed to any occupational exposure is only ~4%–11% (45).

Other widespread factors have been suggested: a diet rich in proteins and fats (46, 47); UV radiation (9, 48); and medical drugs such as painkillers, antibiotics, and corticoids (49). All these exposures call for further investigation, as long as the etiology of NHL remains largely unknown. In the United States, after taking into account all known factors that might have influenced the observed trend, a substantial amount of the total rise (80%) remained unexplained (45).

To sum up, Navarre and Zaragoza registered a major increase in NHL incidence. To a considerable extent, this may have been attributable to improvements in diagnosis, yet the cohort effect suggests a real upsurge. Different widespread exposures with immunosuppressor activity might be producing this change. Additional knowledge on the etiology of NHL is urgently needed to prevent the growing numbers of cases that are expected in years to come.
development of non-Hodgkin's lymphoma in patients with severe human immuno


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