Incidence of Non-Hodgkin’s Lymphoma in Sweden, Denmark, and Finland from 1960 through 2003: an Epidemic That Was

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Abstract

Background: Reports during the early 1990s indicated non-Hodgkin’s lymphoma (NHL) as one of the most rapidly increasing malignancies. More recent trends remain poorly characterized, as do the underlying reasons for NHL time trends, in particular, the effect of changes in classification and registration of lymphoproliferative malignancies. Insights into the descriptive epidemiology of NHL may shed light upon its elusive etiology.

Methods: We used data from the Swedish, Danish, and Finnish national cancer registers to assess the incidences of NHL and other lymphoproliferative malignancies between 1960 and 2004. Using Poisson regression, we estimated the annual rate of change in NHL incidence per decade by sex, age, and country.

Results: In Sweden, Denmark, and Finland, the NHL incidence increased in both genders and all age categories by about 4% every year up until the early 1990s. Thereafter, the incidence increased at a slower rate (ages 60-79 years), stabilized (ages 50-59 and ≥80 years), and decreased (ages 0-49 years), respectively, similarly for males and females in the three countries. Time trends of NHL were not reciprocated and explained by trends for other lymphoproliferative malignancies nor explained by trends in NHL as secondary primaries or NHL diagnosed post-mortem.

Conclusions: The epidemic increase of NHL has recently subsided. Changes in the classification of lymphoproliferative malignancies, or occurrence of NHL as second primaries, only offer a marginal explanation.

Introduction

A remarkable increase in the incidence of non-Hodgkin’s lymphomas (NHL) has been observed during the second half of the 20th century, almost ubiquitous and for as much as long as official statistics have been available (1-14). In several countries, including the Nordic, NHL has been among the most rapidly increasing malignancies and now accounts for 4% of all new cancer cases in the United States (15, 16). Analyses of U.S. cancer statistics (Surveillance, Epidemiology, and End Results) recently indicated a leveling off of the rate of increase, at least in certain (White) age groups (17, 18). In Europe, any such recent shift in trend remains poorly characterized with respect to magnitude, consistency over age, sex, and country, but if substantiated, any worldwide decline in NHL incidence would clearly be of public health relevance.

NHL belongs to the heterogeneous group of lymphoproliferative malignancies, the classification of which has changed considerably over the years (19). However, the extent to which reported NHL time trends are explained by registration-related changes, such as postmortem diagnostic intensity or reciprocating incidences of other types of lymphoproliferative malignancies, remains little studied (14, 20, 21). NHL may be the most common treatment-induced malignancy (22); yet, it is unknown to which extent the increasing cancer survival, accompanied by an increasing number of NHLs related to the treatment of the first malignancy, in the general population has had an effect on NHL time trends.

The unexplained time trends reflect the limited knowledge about the etiology of NHL (23). In this context, it is important to understand whether the time trends of NHL are related to calendar period (indicative of changes in pertinent risk factors that act uniformly on all age groups) or to birth cohort (indicative of changes in risk factors that act earlier in life or affect successive generations differently).

Using information from three Nordic national cancer registers (24-26), we estimated and compared the incidences of NHL and other lymphoproliferative malignancies to (a) describe past and present variations in NHL incidence according to sex, age, and country; (b) to understand the significance of time trends in related non-NHL malignancies, of NHL as second primaries, and of NHL diagnosed post-mortem; and (c) to assess the relative contributions of calendar period and birth cohort to NHL incidence development.

Patients and Methods

Setting. Sweden, Denmark, and Finland constitute a good setting for studies using longitudinal register data. These countries have an ethnically homogenous (>90% Caucasian) population; health care is offered on a population-based basis; and national cancer registers of high quality have been in operation for decades (24-26).

Study Population. In the Swedish (26), Danish (24), and Finnish (25) cancer registers, we identified all individuals...
diagnosed with either of the following lymphoproliferative disorders according to the International Classification of Diseases-7th Edition (ICD-7) code of each condition in each of the cancer registers: NHL, Hodgkin’s lymphoma, acute lymphocytic leukemia, chronic lymphocytic leukemia, and multiple myeloma. To increase the possibility for detecting diverging time trends, we kept NHL and chronic lymphocytic leukemia separate, which is in contrast to the current classification of lymphoproliferative malignancies (27). Although malignancies are reported (in plain text, through ICD codes and through ICD-O morphology codes) by slightly different mechanisms to the Swedish, Danish, and Finnish cancer registries, and although the classification of NHL has changed over time, each of the registers have centrally recoded each registered malignancy into a classification that has remained constant over time. For instance, although clinicians reporting to the Swedish Cancer Register today report the ICD10 code + name of malignancy in plain text, and data on morphology are reported according to the ICD for Oncology-3rd Edition (ICD-O-3) from the pathologist, and the record at the cancer register is centrally supplemented with the corresponding ICD-7 code. Similar central recordings based on ICD-7 are employed in Denmark and Finland. For each individual, we collected information on date of birth, sex, and date of diagnosis of the lymphoproliferative disorder, whether the lymphoproliferative malignancy was the first malignancy reported for that individual, and whether or not NHL was diagnosed based on findings upon autopsy (Sweden). We used data from 1960 through 2003 (Denmark and Finland) or 2004 (Sweden). In total, our analyses encompassed 41,086 Swedish, 21,319 Finnish, and 21,644 Danish registered cases of NHL, and a total of 100,614 non-NHL lymphoproliferative malignancies in the three countries.

Statistical Methods. To characterize changes in incidence of NHL and the effect of changes in classifications of non-NHL lymphoproliferative malignancies, we calculated annual incidence rates for each type of lymphoproliferative malignancy in each country, with age standardized to the world standard population (ref. 28; Fig. 1A-C). We used Poisson regression to quantify annual changes in incidence of NHL over successive decades stratified by sex, age (5-year categories), and country (Table 1), as well as join-point regression (29) to detect shifts in trends with selection of models based on comparison of Akaike Information Criterion.

To model the relative contributions of birth cohort and calendar period on NHL incidence, we calculated sex-specific, age-specific (5-year categories), and birth cohort–specific (overlapping 10-year bands) incidences of NHL (Fig. 2A-C) and modeled these using Poisson regression. Because there is no unique parameterization of models simultaneously, including age, birth cohort, and calendar period (30), we compared the following sequence of (mean) models (ignoring offset and sex), with $Y$ being the number of NHL cases: (a) $\log(Y) = age$, (b) $\log(Y) = age + linear$, (c) $\log(Y) = age + calendar$ period, (d) $\log(Y) = age + birth$ cohort, and (e) $\log(Y) = age + calendar$ period + birth cohort. The covariates age, calendar period, and birth cohort were all treated as categorical variables. The term “linear” is a continuous covariate representing a linear trend not specified as of birth cohort or calendar period origin. Because of the low incidence of NHL below 30 years of age and to avoid bias due to changes in diagnostic intensity at high ages, or uneven intervals in the three countries, the latter analyses were restricted to individuals aged 30 to 84 years and to data through 2003. We also did pairwise comparisons of slopes of changes, or curvature, in period and cohort effects, respectively. The full analyses and results of the age-period-cohort modeling are available in the Supplementary Data.

Results

Incidence of NHL over Time, by Age, Sex, and Country.
The incidence of NHL increased up until the late 1980s or early 1990s. Thereafter, the rate of increase was markedly lower and no longer statistically significant in Sweden or Denmark (Table 1). In Finland, where the net increase in NHL incidence during the study period was the highest, a leveling off of the incidence rate also occurred, although somewhat later than in Denmark and Sweden (Fig. 1). This overall upward trend pattern was similar in the Swedish and age groups until 1994 (Table 1). The incidence developments during the last calendar period (1994-2003) interval were somewhat different, yet remarkably consistent for males and females: Although the incidence plateaued in the age groups 0 to 29 and 30 to 39 years, there was a significant decrease in NHL incidence in the age group 40 to 49 years, no clear change for the 50 to 59 year age group, weak yet increasing trends in the age groups 60 to 69 and 70 to 79 years, and no clear change in the 80 years of age group.

Consistent with the above results, join-point regression analyses across all ages suggested a shift in trend in 1988, 1990, and 1993 for Denmark, Sweden, and Finland, respectively. From these time points, the incidence development was almost zero in Denmark, zero in Sweden, and only slightly increasing in Finland (see Supplementary Data).

NHL Incidence Trends in Relation to Non-NHL Malignancies, to Second Primaries, and to Postmortem Diagnoses.
Overall, the incidence development of NHL in Sweden and Denmark was not reciprocated by trends in incidence of other lymphoproliferative malignancies combined (Fig. 1). In Finland, the incidence rates of both NHL and of “other lymphoproliferative malignancies” increased up until the late 1970s, whereafter the curves diverged (Fig. 1). For the three countries combined, there was, however, little evidence of reciprocity, and when the annual rates of change in incidence of all lymphoproliferative malignancies (NHL plus non-NHL) were analyzed together, there was still evidence of an increase during the 1980s followed by a leveling off during the 1990s (data not shown).

A total of 3,485 (8.7%) of the Swedish, 2,134 (10.2%) of the Danish, and 2,016 (6.9%) of the Finnish NHLs were diagnosed as second or higher primaries. The shapes of the crude incidence curves for all NHL, for NHL as first primaries, and for NHL as second or higher primaries, respectively, largely mirrored each other although the incidence levels were different (see Supplementary Data). However, although the lowest point estimates for the annual rate of change in NHL incidence were observed during the 1994 to 2003 period both for first primary NHLs (Sweden, +0.4%; Denmark, +0.5%; Finland, +0.8%) and for NHL as second or higher primaries (Sweden, +1.7%; Denmark, +1.3%; Finland, +5.6%), the latter were compatible with a continuing increase in NHL incidence. Overall, 1,815 (4.6%) of the Swedish NHLs were diagnosed partly or only based on autopsy findings. This fraction decreased over time (e.g., from 8.2% in 1974-1978 to 2.7% in 1999-2003) but so did also the corresponding fraction of all non-NHL lymphoproliferative malignancies. The declining incidence of autopsy-detected NHL had virtually no effect on the appearance of the overall NHL time trends (see Supplementary Data).

Relative Contribution of Calendar Period and Birth Cohort on NHL Incidence. All finally fitted models showed an adequate fit (Table 2). In each country, data supported a development of NHL incidence more complex than a mere linear trend over time (Table 2). Models including both calendar period and birth cohort best fitted with the Swedish and Danish data, with the effect of calendar period being more...
pronounced than that of birth cohort (Table 2; Supplementary File). Data from Finland provided evidence of age and period effects but weak evidence of a cohort effect. When sex was added as an interaction term in the models, there was no evidence of effect modification in Sweden or Denmark, whereas models of data from Finland, including the interaction between sex and calendar period, fit data marginally better, suggesting the possibility that the Finnish calendar period trends for males and females might differ (data not shown).

With respect to calendar effect, our age-period-cohort modeling verified the findings from the analyses of annual rate of change and indicated a particularly pronounced decline, or slowing of the rate of increase, in NHL incidence among middle-aged individuals beginning in the early 1990s (see Supplementary Data). Age-specific incidences over successive cohorts are displayed in Fig. 2. The logarithmic scale (Fig. 2) does not highlight the fact that although the relative changes in incidence in the age groups up to 59 years of age were most pronounced, the leveling off of the incidence in all older age groups by far outnumbered the trends in younger individuals in terms of number of cases (see Supplementary Data).

**Figure 1.** Incidences of lymphoproliferative malignancies per 100,000 person-years in Sweden (1960-2004), Denmark (1960-2003), and Finland (1961-2003), adjusted to the World Standard Population. NHL, non-Hodgkin’s lymphoma; MM, multiple myeloma; CLL, Chronic Lymphocytic Leukemia; HL, Hodgkin Lymphoma; ALL, Acute Lymphatic Leukemia; and non-NHL, the combined group of MM, CLL, HL, and ALL.
Table 1. Age-specific annual change (%) in incidence of NHL in Sweden, Finland, and Denmark by sex and age (1964-2003)

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Discussion

This tri-national assessment strongly suggests that the epidemic increase of NHL has subsided consistently in all three countries, in both sexes, and for all age groups. In the age groups of 30 to 59 years, we even observed declining rates of NHL since the early 1990s. Our results thereby critically extend previous European (1, 3-5, 11, 13), U.S. (2, 8, 9), or other (10, 12) characterizations of NHL incidence, which, based on data up until the 1990s, have reported increasing incidences. Our results also extend the recent U.S. finding (based on Surveillance, Epidemiology, and End Results data through 1998) of lower rates of annual increments in NHL incidence in certain (White) age groups since the 1990s (17, 18) and suggest that this recent shift in trend is neither spurious nor an isolated U.S. phenomenon.

In our study, the time-related patterns of NHL incidence were largely similar in Sweden, Denmark, and Finland, although Finland displayed more dramatic increases during the early study period and a later tendency towards leveling off. The age- and sex-specific pattern of NHL time trends was largely similar to that from the United States (17), with declining incidences among young adults, and a persistent, yet attenuated, increase among middle-aged/older adults. Some of the U.S. findings, especially among younger individuals, have been related to HIV/AIDS and the implementation of antiretroviral treatment (31). The prevalence of HIV/AIDS in the Nordic countries is lower than in the United States (32). Data from a Danish AIDS register suggest that during 1984 and 2003, 1.5% of all NHL among males and 0.1% of all NHL among females occurred as part of AIDS.7 HIV/AIDS, therefore, offer only a partial explanation for our observed time trends and hardly explain the leveling off in the age groups in which HIV/AIDS-associated lymphomas constitute a minute fraction of all NHL cases.

Whether, or to what extent, any reported time trends of NHL reflect biology or are due to increased diagnostic awareness, registration-related changes, changes in clinical classification, or other nonbiological factors is an important and debated, yet little studied, issue. In this study, central recoding to a relatively simplistic classification of malignancies (ICD-7) provided longitudinally coherent data but little possibility to assess (e.g., trends by NHL subtype). Importantly, this data allows us to contrast NHL time trends to those of other lymphoproliferative malignancies, only to find little to indicate any overall reciprocity. The continuing increase in NHL incidence during the 1990s in Finland, but not in Sweden and Denmark, concurred with a more pronounced decrease in the Finnish incidence of other lymphoproliferative diseases, particularly multiple myeloma and chronic lymphocytic leukemia, for reasons that remain unclear. We cannot exclude that the tendency towards declining incidences of lymphoproliferative malignancies, particularly in Finland, during the very last few years of our study period is an artifact due to lag in registration. However, comparisons of data extracts from each registry in 2003 and in 2005, respectively, suggested a negligible lag (i.e., difference in the calendar year specific incidences between the two extracts) in the reporting of NHL but a tendency towards a lag in reporting of multiple myeloma and chronic lymphocytic leukemia (data not shown). Other explanations for the time trends assessed in our study (NHL as second or later malignancies, for which we found time trends largely similar to those of NHLs as first primaries albeit with a less pronounced leveling off during the 1990s) and changes in autopsy-detected NHLs (which decreased in numbers) had marginal effect on the overall NHL time trends.

The results of our age, period, and cohort modeling of NHL incidence stress the predominance of calendar period over birth cohort effects, although there was some evidence also of the latter. These results fit with the few previous specific assessments of age, period, and birth cohort effects on NHL time trends based on data through the early (3, 13, 33) or mid-1990s (12). In a U.K. study of 2,678 NHLs diagnosed between 1978 and 1991, McNally et al. compared three different methods of analyzing age-period-cohort effects, which (although somewhat inconsistent) pointed to a period effect more pronounced than a birth cohort effect (3). In a Spanish study of 1,421 NHLs diagnosed between 1973 and 1991, Porrán et al. observed an effect of both calendar period and birth cohort, of which the former was more pronounced than the latter (13). In a study from Canada, Liu et al. evaluated 60,617 NHLs diagnosed between 1970 and 1996 and found a strong calendar period effect and a weak birth cohort effect, which was different for males and females (12). Finally, Holford et al. assessed time trends of NHL in Connecticut from 1935 to 1988 and found evidence of both a calendar period and a birth cohort effect (33).

7 Susan Cowan, personal communication.
A particular strength of our study is its nationwide and population-based setting, which also provided the large number of cases and person-years of observation. The general agreement between data from our three Nordic data sets (and with Surveillance, Epidemiology, and End Results data from the United States; ref. 17) indicates that the observed time trends are unlikely to result from national changes in registry-specific practices of diagnosing, reporting, or coding of NHL, unless these were of equal magnitude and occurred simultaneously in these countries. Despite the heterogeneous nature, and possibly etiology (8), of NHL, our longitudinal assessment was limited to NHL as a single entity. This was because of lack of information on subtypes in the registry data throughout the entire study period and our use of a non-morphologic code to identify cases, varying proportions of cases being coded as unspecified NHL, and low comparability of the historical information on subtypes and modern classification methods.

To summarize, we describe a marked attenuation of the epidemic increase of NHL in the Nordic countries, which especially affected the age strata below 60 years. In terms of interpretation of the NHL time trends, these are compatible with two qualitatively different scenarios. In the first, the tendency towards stabilization of the incidence of NHL reflects a recent “saturation” of the general population exposure to relevant risk factors or full implementation of modern diagnostic procedures. According to this model, we should expect NHL rates to be maintained at their current level. In the second model, exposure and effect of the same widely distributed risk factors have first increased and subsequently

Figure 2. Incidence of NHL per 100,000 person-years by age and birth cohort in Sweden (1964-2004), Denmark, and Finland (1964-2003).
possibly decreased; a reason why we should expect NHL rates to continue their decline. The coming few years will provide further important clues to the yet enigmatic epidemiology of NHL.

References

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