Published in final edited form as:

Int J Occup Environ Health. 2010 ; 16(1): 75–84.

Temporal and Demographic Patterns of Non-Hodgkin's Lymphoma Incidence in Pennsylvania

Yueh-Ying Han, Gregg E. Dinse, and Devra L. Davis

Received from: University of Pittsburgh Cancer Institute, Center for Environmental Oncology, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA (YYH, DLD.); National Institutes of Health, National Institute of Environmental Health Sciences, Biostatistics Branch, Research Triangle Park, NC, USA (GD). This research was supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences. Support to the Center for Environmental Oncology came from the Heinz Endowments, the DSF Charitable Foundation, the University of Pittsburgh Cancer Institute, and the Devra Lee Davis Charitable Foundation.

Abstract

Objective—Our study analyzed temporal and demographic patterns of non-Hodgkin's lymphoma (NHL) incidence in Pennsylvania and compared Pennsylvania time trends with national trends.

Methods—Joinpoint and age-period-cohort analyses summarized sex- and race-specific NHL incidence time trends between 1985 and 2004. Ecologic analysis identified demographic factors associated with age-adjusted county-specific NHL incidence.

Results—NHL incidence in Pennsylvania increased annually 1.6% and 2.5% in white and black men and 1.6% and 3.2% in white and black women. National trends were similar, except for smaller increases in white men. Diffuse lymphoma appeared to be the major contributor to the increases. NHL incidence was higher in Pennsylvania counties with greater percentages of urban residents.

Conclusions—NHL incidence patterns in Pennsylvania were parallel to those seen nationally, with the highest rates occurring in white men and in persons residing in urban areas.

Background

While the incidence of all cancers combined began to decrease in 1992 in the United States (US), non-Hodgkin's lymphoma (NHL) incidence continued to increase (Jemal et al. 2008). With an estimated 66,120 new cases and 19,160 deaths projected for the year 2008, NHL is the fifth most common malignant neoplasm among men and women in the US (American Cancer Society 2008). NHL has also increased dramatically in other industrial nations over the past few decades, including Canada (Liu et al. 2003), Australia (Grulich et al. 2005), Sweden, Denmark, Finland (Sandin et al. 2006), and other European countries (Adamson et al. 2007). Increases in NHL incidence were also observed on a smaller scale within state cancer registries in the US. Among Pennsylvania residents, 3300 new cases and 1160 deaths from NHL are expected for the year 2008, with age-adjusted incidence rates in 2000–2004 of 24.7 per 100,000 men and 17.1 per 100,000 women, which are about 6–8 percent higher than the US rates of

Send correspondence to: Yueh-Ying Han, University of Pittsburgh Cancer Institute, Center for Environmental Oncology Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 5150 Centre Avenue, Pittsburgh, PA 15232 USA; hany2@upmc.edu.

Conflict of Interest Statement

None of the authors has any conflicts of interest.

22.8 per 100,000 men and 16.2 per 100,000 women (American Cancer Society 2008). Between 1995 and 2004, age-adjusted NHL incidence was increasing among white and black men and women in Pennsylvania (Pennsylvania Department of Health 2008).

NHL risk has been linked to altered immunity, especially Human Immunodeficiency Virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) (Grulich et al. 2007). Increased risk of NHL has been attributed to certain environmental exposures, such as pesticides and solvents (Boffetta et al. 2007; Hartge et al. 2007). Phenoxy herbicide and 2,4-Dichlorophenoxyacetic acid (2,4-D), two widely utilized agricultural chemicals, have been consistently associated with higher NHL risk (Eriksson et al. 2008; Fisher et al. 2004). Research has indicated the risk factors for NHL vary according to histologic subtypes (Groves et al. 2000), which vary with geography, race, and environmental factors (Muller et al. 2005). Reasons for the rise in NHL incidence are not fully understood. Regardless of histologic subtypes, the impact of changes in case ascertainment and diagnostic practice on overall NHL incidence trends is thought to be small (Clarke et al. 2004). Patterns of NHL incidence might reflect changes in ICD-O coding. A study evaluating the reliability of the SEER ICD-O-2 to ICD-O-3 code conversion algorithm found an overall reliability of 77% for the translation (Clarke et al. 2006). Given the unexplained increases in NHL incidence, researchers continue to investigate possible external causes, including environmental and occupational exposures.

The primary goal of this study was to relate sex- and race-specific NHL incidence rates in Pennsylvania to age, calendar year, birth cohort, and histologic subtype, as well as to investigate the effects of sex, race, occupation, urbanization, and AIDS on age-adjusted, county-specific NHL incidence in Pennsylvania. Specifically, we examined time trends in NHL incidence rates to identify sex, race, and subtype differences. Also, with an aim toward generating etiologic hypotheses and speculating about possible underlying causes of NHL, we performed an ecologic analysis to evaluate certain demographic factors. For example, the two major metropolitan areas of Pennsylvania are Philadelphia and Pittsburgh, where AIDS rates are higher in the former than in the latter. To address issues regarding rural-urban differences and the impact of AIDS, we used county-specific NHL incidence rates to compare Philadelphia, Pittsburgh, and other areas.

A secondary goal of our study was to identify similarities and differences between NHL incidence rates in Pennsylvania and those in the entire US, where the national rates were obtained from a large population-based registry that does not include Pennsylvania. Similarities between Pennsylvania and US patterns provide reassuring confirmation that the observed NHL patterns are real and believable. On the other hand, different incidence patterns provide potential clues about where to direct our future efforts, as we might naturally want to focus on possible NHL risk factors that differ between the two populations.

Materials and Methods

Data Sources

Information on newly diagnosed NHL cases in Pennsylvania from 1985 to 2004 was based on data from the Pennsylvania Cancer Registry (PCR), obtained from the Pennsylvania Department of Health. With the University of Pittsburgh Institutional Review Board exempting the study from review, we requested anonymous patient ID, sex, race, age at diagnosis, year of diagnosis, primary site, ICD-O-3 histology code, and individual Federal Information Processing Standards (FIPS) county codes from the PCR Expanded Incidence File (EIF). Nationwide data on NHL were obtained from the Surveillance, Epidemiology and End Results (SEER) program (Surveillance Epidemiology and End Results (SEER) Program 2007). Specifically, we used data from the SEER 9 registries, which include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; the metropolitan areas of Atlanta, Detroit, and San

Francisco-Oakland; and 13 counties in the Seattle-Puget Sound area. These SEER registries cover 9.5% of the total US population and do not include any areas in Pennsylvania.

The PCR adopted rules from SEER to determine multiple primaries and used ICD-O-3 histology codes to recode the NHL cases. We used the SEER*Prep software (version 2.3.5, <http://seer.cancer.gov/seerprep/index.html>) to convert case-level data in the PCR EIF to the SEER*Stat (version 6.3.5, <http://seer.cancer.gov/seerstat/index.html>) database format, allowing data analysis with SEER*Stat software. NHL case and population counts were aggregated into thirteen 5-year age groups (from 20–24 to 80–84) and four 5-year time periods (from 1985–1989 to 2000–2004) according to sex and race (white and black). Each incidence rate was expressed as the number of NHL cases per 100,000 persons at risk and was age-adjusted relative to the US 2000 standard population.

Similar to the classification used by Groves et al. (Groves et al. 2000), NHL subtypes were classified according to the Working Formulation (WF), which was developed for prognostic purposes. Although the Revised European American classification of Lymphoid Neoplasms (REAL)/WHO system developed in 1994 includes information on immunophenotype and is now used in clinical settings, it was not incorporated into ICD-O until the release of the third edition (ICD-O-3) in 2001 and the etiology of most NHL immunophenotypes is not well known. Moreover, using the Iowa SEER registry data, researchers found 57% – 63% agreement among expert pathologists in classifying NHL cases according to WF and 77% agreement among SEER Program coders in assigning ICD-O codes to cases (Clarke et al. 2004). We categorized ICD-O-3 codes into six major NHL subtypes: small lymphocytic, follicular, diffuse, high-grade, peripheral T-cell, and not otherwise specified (NOS). Information on newly diagnosed NHL cases in the US was obtained from SEER*Stat and analyses similar to those applied to the PCR data were conducted. To match the PCR data, we only used SEER data from 1985 to 2004.

Adjustment for reporting delay in cancer trend analyses can correct underreported cancer cases, especially for persons diagnosed in recent years. Delay-adjusted models produced by the National Cancer Institute (NCI) (Clegg et al. 2002) were used to correct current NHL counts in the SEER registries (<http://srab.cancer.gov/delay/canques.html>). Pennsylvania county population estimates were obtained from the NCI (<http://seer.cancer.gov/popdata/download.html>) and were used to estimate age-adjusted county-specific NHL incidence. The two highest population urban areas of Pennsylvania are Pittsburgh and Philadelphia, which are located in Allegheny County and Philadelphia County. We compared age-adjusted NHL incidence patterns among Allegheny County, Philadelphia County, and all other Pennsylvania counties combined. County-specific US 1990 and 2000 census estimates, including the percentage of the population that is white, the number of males per 100 females, the percentage of civilians aged 16 years and over who work in the farming, fishing and forestry industries, and the percentage of the population living in urban areas were retrieved and averaged (United States Census Bureau). We obtained the cumulative number of AIDS cases (not including HIV infection without AIDS) in Pennsylvania from 1980 to 2004 by county of residence from the Pennsylvania Department of Health (Pennsylvania Department of Health 2007). Average annual AIDS incidence was calculated on the basis of county-specific cumulative cases and population sizes.

Statistical Analysis

We used Poisson regression to perform three different analyses. One analysis is based on joinpoint regression, using software from the NCI (<http://srab.cancer.gov/joinpoint/>). This approach fits line segments, with unspecified joinpoints, to model the logarithms of age-adjusted NHL incidence rates as piecewise-linear functions of time. The NCI software calculates the optimal number of joinpoints and their locations, as well as the estimated annual

percent change (EAPC) within the time interval associated with each line segment (Kim et al. 2000). Separate analyses were conducted for each sex-race group, in both the Pennsylvania and SEER registries.

We also employed Poisson regression to perform age-period-cohort (APC) analyses (Breslow 1984; Dinse et al. 1999; Holford 1983), using SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA). This second approach expresses sex- and race-specific NHL incidence rates as log-linear functions of individual age groups, time periods, and birth cohorts. We estimated the average annual percentage change (AAPC) (Dinse et al. 1999) as an indication of long-term trend over the entire 20-year time span. If the residuals were over-dispersed, based on the Pearson goodness-of-fit chi-squared statistic at the 0.05 level, we used a method developed by Breslow (Breslow 1984) to allow for extra-Poisson variation.

Finally, in a third analysis, we used Poisson regression to assess the importance of several demographic factors. In particular, we investigated whether county-specific information on sex, race, occupation, urbanization, and AIDS incidence was associated with NHL incidence between 1985 and 2004. For each county, we multiplied the population size by the age-adjusted NHL incidence (and divided by 100,000) to obtain an approximate “age-adjusted” number of NHL cases. This ecologic analysis also used SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA), and we included a scale factor in Proc Genmod to account for extra-Poisson variation.

All three analyses were based on Poisson regression, but each model focused on different aspects of how NHL incidence relates to various explanatory variables. The joinpoint analysis allows trends to vary over time, but is adjusted for age through a simple weighted average and is not adjusted for birth cohort or demographic factors. The APC analysis is adjusted for individual age groups, time periods, and birth cohorts, but summarizes trend through a single slope and does not adjust for demographic factors. Finally, the ecologic analysis provides rough assessments of which demographic factors are important, but adjusts for age through a simple weighted average and does not adjust for time period or birth cohort.

Results

Time trends in age-adjusted NHL incidence rates, as estimated under the joinpoint model, are shown in Figure 1, along with EAPC values that significantly differ from zero. Regardless of race or cancer registry, single continuous lines were sufficient to summarize the NHL trends in women, but one or more joinpoints were required to adequately summarize the trends in men. Among women, the PCR trend lines were very similar to the SEER trend lines; among men, the registry-specific trend lines were less similar though still somewhat parallel. On average, the annual increases in NHL incidence among white women were 2.0% in Pennsylvania and 1.5% nationwide; the respective increases among black women were 2.6% and 2.4%. Among black men, NHL rates rose rapidly between the mid-1980s and the early 1990s, with annual increases of 7.4% in Pennsylvania and 7.8% nationwide, and leveled out thereafter. The steep slope between 2002 and 2004 for black men in SEER is not statistically significant. Among white men in Pennsylvania, NHL incidence rose 2.6% annually until 1997 and then increased more slowly in later years. The highest NHL rates were among white men in the SEER registry, though the slopes of the largest line segments were similar to those in the PCR, with an annual increase of 2.1% between 1987 and 1995. For both men and women, NHL incidence rates were higher in whites than blacks.

As illustrated in Figure 2, the APC model seems to fit reasonably well, in the sense that the observed NHL incidence rates for whites are fairly similar to those predicted under the APC model. Plots for blacks are not shown because the smaller population sizes created too much

variability. The age-specific incidence rates appeared to increase over time among white men and women of age 65 years or older. Among white men younger than age 45, NHL incidence rates were higher in the SEER registry than in the PCR. Incidence rates appeared to decrease since 1990–94 among white men in the SEER registry under age 55, except in the youngest age group. Estimates of the long-term linear trend under the APC model are summarized by the AAPC values in Table 1. On average, between 1985 and 2004, the annual increases in NHL incidence rates in Pennsylvania were 1.6% in white men, 2.5% in black men, 1.6% in white women, and 3.2% in black women. The corresponding increases in the SEER registry were 0.3%, 2.2%, 1.4%, and 3.2%, respectively. The average annual increases in the two cancer registries are parallel, excepting for white men where the slope is steeper in Pennsylvania (as indicated by non-overlapping confidence intervals).

In Pennsylvania between 1985 and 2004, a joinpoint analysis suggested the incidences of diffuse and follicular NHL were highest in white men, whereas high-grade NHL incidence was highest in black men (data not shown). Incidence of diffuse NHL was the highest among the six NHL subtypes and the rate increased over time across both the Pennsylvania and SEER registries (Figure 3). In Pennsylvania, the incidence of diffuse NHL increased 3.7% annually in white men and 4.0% in white women between 1990 and 2004. Incidence of follicular and peripheral T-cell NHL increased over time among white men, whereas follicular NHL incidence among white women increased (EAPC = 4.3%) until the mid-1990s and then decreased (EAPC = -3.7%). Incidence of small lymphocytic NHL appeared to be stable during the study period. Incidence of high-grade and NOS NHL appeared to decrease in the 1990s. The patterns of NHL incidence by subtype in the SEER registry are qualitatively similar to those in Pennsylvania, though they differ with respect to the magnitudes of the annual percent changes.

In Philadelphia County, NHL incidence in men increased 6.8% annually between 1985 and 1992 and then leveled off (Figure 4). In women, NHL incidence increased 3.2% annually from 1985 to 1997, and dropped thereafter. In contrast, in Allegheny County, where Pittsburgh is located, NHL incidence significantly increased throughout the study period (EAPC=2.3% in men and 2.7% in women). For all other Pennsylvania counties combined, NHL incidence in women rose 1.6% annually over the entire 20-year time span, whereas in men it rose 2.7% annually between 1985 and 1998 and then leveled off.

Among all 67 Pennsylvania counties combined, the average percentage of whites was 95%; the average number of males per 100 females was 94; the average percentage of civilians aged 16 years and over who work in the farming, fishing and forestry industries was 1.9%; and the average percentage of the population living in urban areas was 45.3%. The average annual AIDS incidence was 4.2%, with the highest rate in Philadelphia County (43.4%) (data not shown). Our ecologic analysis (Table 2) suggested that, in Pennsylvania, NHL incidence rates increased with the county-specific percentage of residents living in urban areas ($p=0.008$). NHL incidence did not appear to be associated with the percentage of whites, the ratio of males per 100 females, the percentage of adults working in the farming, fishing and forestry industries, or AIDS incidence between 1980 and 2004.

Discussion

Remarkable increases in NHL incidence in the Pennsylvania and SEER registries have occurred over the past two decades, as indicated by our joinpoint and APC analyses. Continual increases in NHL incidence were observed in women and in older age groups, and in both men and women in Allegheny County. In particular, the incidence of diffuse and peripheral T-cell lymphoma has increased significantly over time. In the SEER registries, recent increases in NHL incidence in white men are unexplained. Further data, including information on changes

in population variation and in behavioral, workplace, or other risk factors, are needed to determine what may account for these patterns.

Results from the APC analysis based on SEER NHL incidence were similar to those obtained in a previous study (Dinse et al. 1999), although the rate of increase slowed more recently among men. NHL is one of the major AIDS-associated malignancies highly impacted by the AIDS epidemic in the US (Engels et al. 2006). In the United States, AIDS incidence increased rapidly since 1982, started to level off in 1995, and was highest among people aged 30–49. From 2002 to 2006, a total of 73% of AIDS cases were male and 49% were black (Center for Disease Control and Prevention 2006). Time trends obtained from our joinpoint analysis showed a slowing of NHL rates in black men in both the Pennsylvania and SEER registries, an observation consistent with the decreased HIV/AIDS epidemic and improved treatment in the 1990s. NHL incidence in Philadelphia County, which was heavily impacted by HIV/AIDS, started to decrease in 1992 among men and 1997 among women. Nevertheless, changes in the prevalence of HIV/AIDS cannot explain NHL patterns in the elderly or the recent increase in white men and women.

Higher NHL incidence rates have been linked to altered immunity, such as that associated with transplantation, blood transfusion, and immunosuppression (Chow et al. 2002; Fisher & Fisher 2004; Grulich et al. 2007). Infectious agents such as the Epstein-Barr virus (EBV) are regarded as established causes of NHL, especially in individuals with immune dysfunction (Engels 2007). Between 1971 and the mid-1980s, the number of units of red blood cells and whole blood transfused per unit of population in the US increased over 60 percent, reaching a peak in 1986 and then declining (Chow & Holly 2002; Surgenor et al. 1990). EBV infection is not commonly seen outside of endemic areas, typically in Africa, and mostly is related to Burkitt's lymphomas. Due to growing numbers of organ and tissue recipients (increased from 12,623 recipients in 1988 to 27,038 in 2004, according to data from the US Department of Health and Human Services), the number of patients at risk for NHL is expanding. However, the risk also depends on the intensity of immunosuppressive treatment (Muller et al. 2005). It is unlikely that recent time trends in NHL could reflect changes in these immunological factors.

An extensive literature indicates that the risk of NHL is increased by a number of environmental exposures. Several investigators have proposed a causal relationship between occupational benzene exposure and NHL (Goldstein et al. 1999; Smith et al. 2007; Vineis et al. 2007). Exposures to agricultural chemicals and solvents have been associated with increased NHL risk in studies conducted on the basis of data from several major national cancer registries (De Roos et al. 2003; Fritschi et al. 2005; Hardell et al. 1999; Rafnsson 2006; Schroeder et al. 2001). Survivors of atomic bombs or nuclear reactor accidents have a higher risk of many kinds of cancer, including NHL (American Cancer Society 2009). Cancer incidence in counties near two former nuclear materials processing facilities in Armstrong County Pennsylvania has been studied, but no increase in NHL incidence was found (Boice et al. 2003; Boice et al. 2009).

In addition, NHL risk differs by sex. Continuously increasing NHL incidence among women is unexplained. Use of coal-tar-based, dark hair dyes among women has been associated with NHL development, but the evidence is inconsistent (Takkouche et al. 2005). Zhang and his colleagues recently reported that personal hair-dye use may play a role in risks of follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma in women, especially those who started using hair dye before 1980 (Zhang et al. 2008). Additional studies are needed to examine the risk of NHL by time period of hair-dye use and by genetic susceptibility. An increasing female workforce and occupational exposure in recent decades may also be contributing to persisting increases in women that are occurring worldwide. Future studies of the relationship between environmental exposures and sex-specific NHL incidence,

especially among older groups with long-term exposure to a variety of hematopoietic toxicants, could clarify possible explanations for recently increased rates among those over age 55.

Regarding NHL histologic subgroups, diffuse lymphoma was the main contributor of increased NHL incidence in our study. Occurrence of different NHL subtypes is caused by different risk factors. Industrial workers exposed to electromagnetic fields and metals have a greater risk of diffuse lymphoma (Band et al. 2004; Zheng et al. 2002). Exposures to agricultural chemicals increase risk for diffuse and follicular lymphoma (Band et al. 2004; Eriksson et al. 2008; Fritschi et al. 2005). In the US, total pesticide use rose from 647 million pounds in 1964 to 1144 million pounds in 1979 and then declined to 971 million pounds in 1995 (United States Environmental Protection Agency 1997). The role of occupation and pesticide exposure in the increase of diffuse lymphoma should be carefully examined. Lifestyle factors such as diet, obesity, and physical activity may also account for some variation in NHL subtype (Chang et al. 2006; Chang et al. 2005; Kelemen et al. 2006; Zheng et al. 2004). Specifically, obesity-related NHL risk is greater for diffuse and follicular subtypes (Pan et al. 2005; Skibola et al. 2004; Willett et al. 2008). The number of adults who are overweight or obese has continued to increase in the US. In Pennsylvania, 16% of adults were obese in 1995, a figure that rose to 25% in 2005 (Pennsylvania Department of Health 2006). The extent to which mechanisms in obesity may account for some of the patterns reported here is a matter that should be seriously pursued.

High-grade NHL, a subtype associated with 90% of AIDS-related NHL, was the most rapidly increasing subtype in 1985–1990, particularly among men (Groves et al. 2000). In recent years, declines in the incidence of high-grade NHL in the Pennsylvania and SEER registries may reflect corresponding declines in the AIDS epidemic. However, high-grade NHL incidence was highest in black men (data not shown), which may result from delayed diagnosis. Recent decreases in not-otherwise-specified NHL may be due to improved histologic diagnosis of lymphoma. Findings from our population-based study provide evidence that incidence trends vary with NHL subtypes and depend on certain demographic patterns. As diagnostic techniques improve, future investigations should evaluate NHL risk according to subtype. Comparisons with past trends may be challenging, however, as histologic classifications change over time.

In Pennsylvania, we found that populations living in urbanized counties had significantly higher risks of NHL, and that greater rates of increase occurred in white men, many of whom reside in urban areas. In Allegheny County, the metropolitan area surrounding the City of Pittsburgh, NHL incidence increased over time in both men and women. Similarly, Devesa *et al* found that NHL incidence was lower in rural areas (Devesa et al. 1992; Muller et al. 2005). Although it is not possible to attribute the ecologic relationship between urbanization and increased NHL to a causal association, differences in urbanization as well as obesity might be relevant to NHL risk in the entire US. Percent of total population living in an urban area has increased 23% from 1950 to 2000 (64% in 1950 and 79% in 2000) (United States Census Bureau). The recent increases in the prevalence of overweight and obesity are reflected across all ages, racial and ethnic groups, and education levels in the US (Center for Disease Control and Prevention 2004). Characteristics of urban living, such as population density and structure, poor diet and obesity, lifestyle, development process and socioeconomic factors, should be studied to identify NHL risk factors and to account for NHL geographic distributions in Pennsylvania.

Conclusions

Although the time course of NHL occurrence is not well explained, increased NHL incidence patterns observed in Pennsylvania generally paralleled those observed nationally in the SEER registries. NHL incidence increased over time among men and women in Allegheny County,

while it initially increased and then leveled off in the 1990s in Philadelphia County. A number of studies should be carried out to identify the factors that may account for these patterns. Sex-specific risk factors should be investigated that may account for persisting unexplained increases in NHL among women, including environmental and workplace exposures and changes of lifestyle. Future work should explore what aspects of urbanization may contribute to the apparent increased risk of NHL that we have found.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences. Support to the Center for Environmental Oncology came from the Heinz Endowments, the DSF Charitable Foundation, the University of Pittsburgh Cancer Institute, and the Devra Lee Davis Charitable Foundation. Ethics committee approval was not required for the study. The relevant Institutional Review Boards designated our study as exempt. The authors appreciate the constructive comments of Grace Kissling and David Umbach.

References

- Adamson P, Bray F, Costantini AS, et al. Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe. *Eur J Cancer* 2007;43 (2):391–401. [PubMed: 17134891]
- American Cancer Society. Cancer Statistic for 2008: Cancer Facts & Figures 2008. Leading Sites of New Cancer Cases and Deaths – 2008 Estimates. 2008 [cited 2008 July 15].
- American Cancer Society. Overview: Lymphoma, Non-Hodgkin Type. What Causes Non-Hodgkin Lymphoma?. 2009 [cited 2009 July 20].
- Band PR, Le ND, Fang R, et al. Identification of occupational cancer risks in British Columbia: a population-based case-control study of 769 cases of non-Hodgkin's lymphoma analyzed by histopathology subtypes. *Journal of Occupational & Environmental Medicine* 2004;46 (5):479–89. [PubMed: 15167397]
- Boffetta P, de Vocht F. Occupation and the risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007;16 (3):369–72. [PubMed: 17372232]
- Boice JD Jr, Bigbee WL, Mumma MT, et al. Cancer incidence in municipalities near two former nuclear materials processing facilities in Pennsylvania. *Health Phys* 2003;85 (6):678–90. [PubMed: 14626319]
- Boice JD Jr, Bigbee WL, Mumma MT, et al. Cancer incidence in municipalities near two former nuclear materials processing facilities in Pennsylvania--an update. *Health Phys* 2009;96 (2):118–27. [PubMed: 19131733]
- Breslow NE. Extra-Poisson Variation in Log-linear Models. *Applied Statistics* 1984;33 (1):38.
- Center for Disease Control and Prevention. Health, United States, 2004. National Center for Health Statistics, National Health and Nutrition Examination Survey. 2004 [cited 2008 October 10].
- Center for Disease Control and Prevention. HIV/AIDS Surveillance Report: Cases of HIV Infection and AIDS in the United States and Dependent Areas. 2006. [cited 2008 April 08]
- Chang ET, Balter KM, Torrang A, et al. Nutrient intake and risk of non-Hodgkin's lymphoma. *Am J Epidemiol* 2006;164 (12):1222–32. [PubMed: 17005624]
- Chang ET, Smedby KE, Zhang SM, et al. Dietary factors and risk of non-hodgkin lymphoma in men and women. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14 (2):512–20.
- Chow EJ, Holly EA. Blood transfusions and non-Hodgkin's lymphoma. *Epidemiologic Reviews* 2002;24 (2):269–79. [PubMed: 12762097]
- Clarke CA, Glaser SL, Dorfman RF, et al. Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: reliability of diagnosis and subtype classifications. *Cancer Epidemiology, Biomarkers & Prevention* 2004;13 (1):138–43.
- Clarke CA, Undurraga DM, Harasty PJ, et al. Changes in cancer registry coding for lymphoma subtypes: reliability over time and relevance for surveillance and study. *Cancer Epidemiol Biomarkers Prev* 2006;15 (4):630–8. [PubMed: 16614102]
- Clegg LX, Feuer EJ, Midthune DN, et al. Impact of reporting delay and reporting error on cancer incidence rates and trends. *J Natl Cancer Inst* 2002;94 (20):1537–45. [PubMed: 12381706]

- De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 2003;60 (9):E11. [PubMed: 12937207]
- Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res* 1992;52 (19 Suppl):5432s–40s. [PubMed: 1394149]
- Dinse GE, Umbach DM, Sasco AJ, et al. Unexplained increases in cancer incidence in the United States from 1975 to 1994: possible sentinel health indicators? *Annu Rev Public Health* 1999;20:173–209. [PubMed: 10352856]
- Engels EA. Infectious agents as causes of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007;16 (3):401–4. [PubMed: 17337646]
- Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *Aids* 2006;20 (12):1645–54. [PubMed: 16868446]
- Eriksson M, Hardell L, Carlberg M, et al. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *International Journal of Cancer* 2008;123 (7):1657–63.
- Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene* 2004;23 (38):6524–34. [PubMed: 15322522]
- Fritschi L, Benke G, Hughes AM, et al. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. *American Journal of Epidemiology* 2005;162 (9):849–57. [PubMed: 16177143]
- Goldstein, BD.; Witz, G. Chapter 4: Benzene. In: Lipman, M., translator and editor. *Environmental Toxicants: Human Exposure and Their Health Effects*. 2. John Wiley and Sons; 1999. p. 121-50.
- Groves FD, Linet MS, Travis LB, et al. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *Journal of the National Cancer Institute* 2000;92 (15):1240–51. [PubMed: 10922409]
- Grulich AE, Vajdic CM. The epidemiology of non-Hodgkin lymphoma. *Pathology* 2005;37 (6):409–19. [PubMed: 16373224]
- Grulich AE, Vajdic CM, Cozen W. Altered immunity as a risk factor for non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007;16 (3):405–8. [PubMed: 17337643]
- Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 1999;85 (6):1353–60. [PubMed: 10189142]
- Hartge P, Smith MT. Environmental and behavioral factors and the risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007;16 (3):367–8. [PubMed: 17344463]
- Holford TR. The estimation of age, period and cohort effects for vital rates. *Biometrics* 1983;39 (2):311–24. [PubMed: 6626659]
- Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. *J Natl Cancer Inst* 2008;100 (23):1672–94. [PubMed: 19033571]
- Kelemen LE, Cerhan JR, Lim U, et al. Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute-Surveillance, Epidemiology, and End Results population-based case-control study. *Am J Clin Nutr* 2006;83 (6):1401–10. [PubMed: 16762953]
- Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19 (3):335–51. [PubMed: 10649300]
- Liu S, Semenciw R, Mao Y. Increasing incidence of non-Hodgkin's lymphoma in Canada, 1970–1996: age-period-cohort analysis. *Hematological Oncology* 2003;21 (2):57–66. [PubMed: 12802810]
- Muller AM, Ihorst G, Mertelsmann R, et al. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Annals of Hematology* 2005;84 (1):1–12. [PubMed: 15480663]
- Pan SY, Mao Y, Ugnat AM, et al. Physical activity, obesity, energy intake, and the risk of non-Hodgkin's lymphoma: a population-based case-control study. *American Journal of Epidemiology* 2005;162 (12):1162–73. [PubMed: 16269580]
- Pennsylvania Department of Health. 2005 Behavioral Risks of Pennsylvania Adults. 2006. [cited 2007 April 20]
- Pennsylvania Department of Health. Bureau of Epidemiology and Health Statistics & Research, HIV/AIDS Surveillance Biannual Summary. 2007. [cited 2007 April 04]

- Pennsylvania Department of Health. Health Statistics and Research, Pennsylvania Cancer Incidence and Mortality 2004. 2008. [cited 2008 July 15]
- Rafnsson V. Risk of non-Hodgkin's lymphoma and exposure to hexachlorocyclohexane, a nested case-control study. *Eur J Cancer* 2006;42 (16):2781–5. [PubMed: 16934973]
- Sandin S, Hjalgrim H, Glimelius B, et al. Incidence of non-Hodgkin's lymphoma in Sweden, Denmark, and Finland from 1960 through 2003: an epidemic that was. *Cancer Epidemiol Biomarkers Prev* 2006;15 (7):1295–300. [PubMed: 16835326]
- Schroeder JC, Olshan AF, Baric R, et al. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology* 2001;12 (6):701–9. [PubMed: 11679800]
- Skibola CF, Holly EA, Forrest MS, et al. Body mass index, leptin and leptin receptor polymorphisms, and non-hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2004;13 (5):779–86. [PubMed: 15159310]
- Smith MT, Jones RM, Smith AH. Benzene exposure and risk of non-Hodgkin's lymphoma. *Cancer Epidemiology Biomarkers and Prevention* 2007;16 (3):385–91.
- Surgenor DM, Wallace EL, Hao SH, et al. Collection and transfusion of blood in the United States, 1982–1988. *N Engl J Med* 1990;322 (23):1646–51. [PubMed: 2342524]
- Surveillance Epidemiology and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 9 Regs, Nov 2006 sub (1973–2004). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2007. SEER 1973–2004 public use data. (www.seer.cancer.gov)released April 2007, based on the November 2006 submission
- Takkouche B, Etminan M, Montes-Martinez A. Personal use of hair dyes and risk of cancer: a meta-analysis. *Jama* 2005;293 (20):2516–25. [PubMed: 15914752]
- United States Census Bureau. Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995 to 2050, U.S Bureau of the Census, Current Population Reports. [cited 2007 March 27]
- United States Environmental Protection Agency. Pesticides industrial sales and usage: 1994–1995 Pesticide market estimates: Tables and Charts. 1997. [cited 2007 July 07]
- Vineis P, Miligi L, Costantini AS. Exposure to solvents and risk of non-Hodgkin lymphoma: clues on putative mechanisms. *Cancer Epidemiol Biomarkers Prev* 2007;16 (3):381–4. [PubMed: 17337640]
- Willett EV, Morton LM, Hartge P, et al. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. *International Journal of Cancer* 2008;122 (9):2062–70.
- Zhang Y, Sanjose SD, Bracci PM, et al. Personal use of hair dye and the risk of certain subtypes of non-Hodgkin lymphoma. *American Journal of Epidemiology* 2008;167 (11):1321–31. [PubMed: 18408225]
- Zheng T, Blair A, Zhang Y, et al. Occupation and risk of non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *J Occup Environ Med* 2002;44 (5):469–74. [PubMed: 12024692]
- Zheng T, Holford TR, Leaderer B, et al. Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut women. *American Journal of Epidemiology* 2004;159 (5):454–66. [PubMed: 14977641]

Figure 1.

Joinpoint estimates of NHL incidence in the PCR and SEER registries by sex and race for persons diagnosed from 1985 to 2004 at ages 20 to 84, adjusted for age and reporting delays (EAPC values that differ significantly from zero are indicated).

Figure 2.

NHL incidence (on a log scale) in the PCR and SEER registries by age group and time period for white men and women diagnosed from 1985 to 2004 at ages 20 to 84, adjusted for reporting delays. The X's are observed values and the lines are predicted values based on an APC model with 5-year age and period intervals.

Figure 3.

Joinpoint estimates of NHL incidence in the Pennsylvania and SEER registries by sex, year of diagnosis, and histologic subtype of the Working Formulation for whites diagnosed from 1985 to 2004 at ages 20 to 84, adjusted for reporting delays and age adjusted to the 2000 US standard population (EAPC values that differ significantly from zero are indicated).

Figure 4.

Joinpoint estimates of NHL incidence in the PCR by sex and county for persons diagnosed from 1985 to 2004 at ages 20 to 84, adjusted for age and reporting delays (EAPC values that differ significantly from zero are indicated).

Results from separate APC models for NHL incidence in the PCR and SEER registries by sex and race for persons diagnosed from 1985 to 2004 at ages 20 to 84, adjusted for reporting delays. The APC analyses used 5-year age and period intervals.

Table 1

Registry	Sex	Race	Model	AAPC	95% C.I.
PCR	Men	White	Poisson	1.55	(1.16, 1.94)
		Black	extra-Poisson	2.49	(1.02, 3.99)
	Women	White	Poisson	1.61	(1.18, 2.05)
		Black	Poisson	3.18	(1.77, 4.61)
SEER	Men	White	extra-Poisson	0.33	(-0.23, 0.89)
		Black	extra-Poisson	2.23	(1.20, 3.27)
	Women	White	Poisson	1.42	(1.17, 1.67)
		Black	extra-Poisson	3.15	(2.05, 4.26)

AAPC - average annual percentage change

C.I.-confidence interval

Table 2

Results from Poisson regression analysis for assessing which county-specific factors are important predictors of NHL incidence in Pennsylvania among persons diagnosed from 1985 to 2004 at ages 20 to 84, adjusted for age, reporting delays, and extra-Poisson variation.

Independent Variables	Regression Coefficient	Standard Error	Chi-squared Statistic ¹	P-value
Constant	-9.0933	0.4333	440.45	<0.001
Race (% white)	0.0055	0.0039	2.02	0.156
Sex (number of men per 100 women)	0.0006	0.0006	1.04	0.307
Occupation (% farmers)	0.0072	0.0172	0.18	0.674
Urbanization (% living in urban area)	0.0021	0.0008	7.03	0.008
AIDS Incidence ²	0.0046	0.0042	1.20	0.273

¹ Each chi-squared statistic is associated with 1 degree of freedom.

² AIDS incidence was calculated on the basis of county-specific accumulated AIDS cases and population sizes, 1980–2004.