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## Time trends in rates of Hodgkin lymphoma histologic subtypes: true incidence changes or evolving diagnostic practice?

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### Abstract

**Background**—Histologic subtypes of classical Hodgkin lymphoma (cHL) (e.g., nodular sclerosis (NS), mixed cellularity (MC), not otherwise specified (NOS)) are epidemiologically and prognostically distinctive. Therefore, unexplained, ongoing incidence rate declines for MC and increases for NOS require examination.

**Methods**—We analyzed detailed histology-specific HL incidence rates in 1992–2011 U.S. SEER data ( $n=21,372$ ) and reviewed a regional subset of 2007–11 NOS pathology reports for insight into diagnostic practices.

**Results**—cHL rates were stable until 2007, then decreased for whites (annual percent change (APC) and 95% confidence interval,  $-3.6\%$  ( $-5.6\%$ ,  $-1.5\%$ )). NS rates declined after 2007 by 5.9% annually, with variation by gender, age, and race/ethnicity. In 1992–2011, MC rates declined (APC  $-4.0\%$  ( $-4.7\%$ ,  $-3.3\%$ )) whereas NOS rates rose (5.3% (4.5%, 6.2%)) overall and in most patient groups. 2007–11 NOS age-specific rates were more similar to MC rates for 1992–96 than 2007–11. Trends in combined rates were minimal, supporting increasing misclassification of MC, LD, and specific NS subtypes as NOS. Eighty-eight of 165 reviewed NOS pathology reports addressed classification choice. Twenty (12.1%) justified the classification, 21 (12.7%) described insufficient biopsy material, and coders missed specific subtype information for 27 (16.4%).

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#### Disclosure of conflicts of interest

None of the coauthors has actual, potential, or perceived conflicts of interest related to this paper

#### AUTHORSHIP CONTRIBUTIONS

Sally Glaser, Christina Clarke and Theresa Keegan designed the study. Sally Glaser, Christina Clarke, Theresa Keegan and Ellen Chang interpreted the results and contributed to manuscript writing and review. Dennis Weisenburger provided pathology expertise and contributed to manuscript writing and review.

**Conclusion**—Recent NS rate declines largely represent true incidence changes. Long-term rate decreases for MC and other less-common subtypes, and increases for NOS (comprising ~30% of cHL cases in 2011), likely reflect changes in diagnostic and/or classification practice.

**Impact**—Diminishing histologic subtyping undermines future surveillance and epidemiologic study of HL. Guideline-based use of excisional biopsies and more coding quality control are warranted.

### Keywords

Hodgkin lymphoma; histologic subtype; incidence; SEER; pathology

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## INTRODUCTION

Hodgkin lymphoma (HL) is a B-cell malignancy with complex, variable pathology (1) that has been classified by several histology schemes over time (2, 3). The 1966 “Rye” modification of the Lukes-Butler classification, which described reproducible, clinically correlated subtypes (nodular sclerosis (NS), mixed cellularity (MC), lymphocyte depletion (LD), lymphocyte predominance (LP)), was used for nearly 30 years (1, 2). In 1994, the Revised European-American Lymphoma (REAL) classification differentiated the etiologically distinct nodular LP (nLP) from classical HL (cHL) (4), which comprised NS, MC, LD and the new LP category lymphocyte-rich (LR). In 2001, this schema was accepted in the World Health Organization (WHO) classification of hematopoietic and lymphoid tumors (3). Its categories are captured by International Classification of Diseases for Oncology (ICD-O) codes, with which tumor registrars code HL histologic subtypes based on pathology reports (5).

In addition to having biological and prognostic differences (2, 3, 6–10), HL histologic subtypes show considerable epidemiologic variation (1, 11–18). For NS, the most common cHL subtype, incidence rates have been relatively stable over time (12, 19, 20), whereas studies have documented persistently declining rates for MC (12, 20, 21) and increasing rates of cHL not otherwise specified (12, 20), an ICD-O-3 category designating cHL without further histologic subtyping (hereafter called NOS). For MC, the second most common cHL subtype in the western world, decreasing rates could signal changes in the prevalence of risk factors (12, 21, 22), including lower socioeconomic status (23, 24), HIV infection (25), other immunosuppression (26, 27), and smoking (28); and in factors leading to the presence in some tumors of Epstein-Barr virus (EBV) (29, 30). For NOS, rate increases may reflect changes in diagnostic practice (e.g., use of smaller biopsies rendering precise diagnoses difficult) and/or in histologic classification (e.g., increasing reliance on cHL as the terminal category), leading to incorporation of cases that previously would have been coded as more specific histologic subtypes.

As histologic heterogeneity is central to HL etiology and the accurate monitoring of its occurrence, understanding the persistent yet unexplained incidence trends for MC and NOS is important. Therefore, we evaluated detailed HL incidence rates by histologic subtype over the past 20 years, using population-based U.S. National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) cancer registry data to provide the large case series

needed for informative study of this uncommon disease. Further, for insight into diagnostic and classification issues pertinent to NOS rate increases, we reviewed diagnostic pathology reports for a regional subset of NOS cases.

## MATERIALS AND METHODS

We identified all new cases of primary cHL (ICD-O, 3<sup>rd</sup> Edition, morphology codes 9663–9667 (NS); 9652 (MC); 9651 (LR); 9653 (LD); 9650 (NOS)) and nLP (code 9659) diagnosed in the years 1992 through 2011 and included in the SEER 13 database (31). This database provides broad geographic coverage across 13 U.S. states and metropolitan areas, and data by detailed racial/ethnic groups (i.e., non-Hispanic white, Hispanic, non-Hispanic black, non-Hispanic Asian/Pacific Islander, and American Indian/Alaska Native, hereafter called white, Hispanic, black, API and AI/AN), which have differing HL epidemiologic profiles (11, 23, 24). For all 21,372 HL cases, we obtained registry data routinely abstracted or derived from the medical record on patient age, gender, race/ethnicity, tumor histology coded to ICD-O-3, tumor site, disease stage, and reporting SEER registry from the time of diagnosis.

To obtain information about recent diagnostic and classification practices for NOS, we used data from a quality-control review at the Greater Bay Area Cancer Registry (a participant in the SEER program) of all 286 incident HL cases reported to SEER as NOS for the diagnosis years 2007–11 (a period chosen because of the availability of pathology reports submitted to the registry electronically). Among these cases, the 165 (57.7%) with electronic pathology reports and reviewed by a registry quality-control specialist did not differ significantly from the 121 not reviewed, according to chi-square tests, by age (four groups,  $p=0.11$ ), gender ( $p=0.21$ ), race/ethnicity ( $p=0.22$ ), tumor site ( $p=0.55$ ), or disease stage ( $p=0.37$ ), but did differ by year of diagnosis ( $p<0.001$ ), due to increasing electronic reporting over time. From the pathology report text, the reviewer classified each NOS diagnosis by factors related to diagnostic practice. These included justification of the NOS classification, indication of specimen inadequacy for subtyping, subtype specification with insufficient definitiveness for coding per SEER requirements (32), subtype specification missed by coding registrars, biopsy type (excisional, core/fine needle aspiration (FNA)), biopsy site (lymph node, bone marrow), diagnosis facility (NCI-designated cancer center, integrated health system, other), location of final diagnosis (original diagnosing hospital, outside consultation), and existence of additional diagnostic studies.

### Statistical Analysis

We computed average annual age-adjusted (to the 2000 US standard million population) HL incidence rates per 100,000 population and 95% confidence intervals (CI) for cHL overall, nLP, and cHL subtypes (as defined above), as well as for NS subtypes (the predominant category, NS NOS (code 9663), and the remaining categories NS cellular phase, grade 1, and grade 2 (codes 9664–9667)). We calculated rates by 10-year age group to capture HL age heterogeneity, and for the age groups 0–14, 15–39, 40–54 and 55 years and above (called “children”, “adolescents/young adults (AYAs)”, “middle-aged adults” and “older adults”) to accommodate etiologic differences (33). We also calculated rates by gender, race/ethnicity

(because of small numbers, we do not present AI/AN rates), stage (localized, regional, distant, unknown), tumor site (nodal, extranodal), year of diagnosis, and reporting SEER registry.

To evaluate time trends, we calculated annual incidence rates and conducted Joinpoint (segmented linear) regression analysis, which identifies specific significant changes in annual rates over time and calculates the annual percent change (APC) and associated 95% CI in rates within each trend segment (34). We also calculated incidence rates for four five-year time periods (1992–96, 1997–2001, 2002–06, 2007–11) for cHL, cHL subtypes and nLP (Supplemental Table 1), and for NS subtype groups (Supplemental Table 2). We compared five-year rates in order to a) summarize the overall magnitude of a change, b) quantify change when sample sizes prevented calculation of an APC, or c) compare rates for two specific five-year periods. For these purposes, we calculated incidence rate ratios (IRRs), considering as significant any differences for which the IRR 95% CI did not include 1; all IRRs presented reflect comparisons to the 1992–96 rate unless otherwise indicated.

To examine the possibility that the previously described opposing incidence trends for MC and NOS rates (12, 20) reflected increasing incorporation of true MC diagnoses into NOS over time, we 1) compared age-specific rates of MC and NOS in the earliest and latest five-year time periods (1992–96, 2007–11), using IRRs to evaluate whether differences in subtype rate patterns diminished, consistent with a case transfer; and 2) calculated rates, and used Joinpoint to examine trends, for MC and NOS combined, postulating that a lack of significant trends for this grouped category would support a case transfer. We repeated both analyses by also combining LD cases, since they may be considered grades of one subtype (2), and the NS subtype group 9664–9667, as pathology practices around their use have changed over time (35, 36).

We characterized NOS diagnostic practice using chi-square or Fisher's exact tests to examine cases by registry patient and tumor characteristics and quality-control study factors, focusing on biopsy type because core/FNA biopsies have been associated with difficulties in diagnosing HL (37)).

We used SEER\*Stat software (38) to calculate rates, Joinpoint Regression Program version 4.0.4 for Joinpoint analyses, and SAS version 9.3 for descriptive statistics. All analyses had the oversight of the institutional review board at the Cancer Prevention Institute of California.

## RESULTS

### Incidence trends for cHL and nLP

Overall age-adjusted incidence rates of cHL were stable until 2007, when they began to decline (Table 1, Figure 1). For whites, they decreased from 2007 at nearly 5% per year, whereas for APIs they rose throughout the study period, although with a plateau suggested in the 2000s (IRR, 2002–06: 1.39 (1.13, 1.70); 2007–2011: 1.36 (1.11, 1.66)). cHL rates decreased for ages 30–39 from 2008 at greater than 8% annually, but rose modestly for ages 80 and older and, starting in 2001, for ages 10–19. Rates decreased for localized disease, but

increased modestly for regional and distant disease. For nodal disease, rates declined at 3.7% annually after 2007, whereas for extranodal disease, they rose throughout the study period.

For nLP, rates increased nearly 6% per year (Table 1), more than doubling between 1992–96 and 2007–11 (IRR: 2.32 (1.89, 2.85)). Increases occurred for both genders, all races (significantly for whites and blacks), all age groups, and all disease stages.

### Incidence trends for cHL subtypes

**NS**—NS rates overall were stable until 2007, then declined 6% on average per year. Table 1 and Figures 2a–d show that rates decreased for females throughout the study period but for males only after 2007 (2a); rates decreased for whites and blacks after 2007–08, did not change for Hispanics, and increased for APIs over the study years (Figure 2b). Rates decreased across most age groups (Figure 2c), at greater than 8% annually under age 10 (from 2001) and at ages 40–49 (from 2006) (Table 1). For AYAs, females experienced a significant, although slight, rate decline throughout (APC for 1992–2011,  $-0.9$  ( $-1.5, -0.4$ )), whereas rates for males suggested a recent drop (APC for 1992–2008,  $0.4$  ( $-0.4, 1.2$ ); 2008–2011,  $-8.3$  ( $-17.9, 2.3$ )). For middle-aged adults, rates declined in 2004 following a modest increase. Rates decreased for localized disease as of 1998. They decreased for nodal disease from 2007, but rose steadily for extranodal disease since 1992.

Table 2 and Figures 3a–d show that for the NS 9663 subtype (comprising 87.5% of all NS cases), rate patterns were quite similar to those seen for NS overall. For the remaining NS subtypes group, significant, large rate declines occurred for males and females (Figure 3e); whites (Figure 3f); AYAs, middle-aged and older adults (Figure 3g); localized and regional stages (Figure 3h); and nodal disease. Many of these declines commenced in the mid 2000s.

**MC**—MC rates decreased over the study period, approximately halving by 2007–11 (IRR: 0.56 (0.5, 0.62)). Figures 2e–h show 3%–6% annual declines for both genders (Figure 2e), all racial/ethnic groups (Figure 2f), all age groups except 0–9 and 20–29 (Figure 2g), and all stages (Figure 2h). APCs showed that rates also declined in almost all regional registries (Table 1).

**LD**—Decreases occurred in rates overall, and for males, whites, older adults, localized and distant stages (IRR, 2007–11: 0.59 (0.36, 0.95)) and nodal disease.

**LR**—LR incidence declined significantly among older adults (Table 1), children (IRR, 2002–06: 0.35 (0.11, 0.93)), and persons ages 20–29 (IRR, 2002–06: 0.53 (0.28, 0.98), IRR, 2007–11: 0.51 (0.27, 0.95)). Rates declined for localized disease throughout and rose for distant-stage disease (IRR, 2007–11: 2.84 (1.22, 7.40)).

**NOS**—Across the study period, NOS rates doubled overall (IRR, 2007–11: 2.19 (1.98, 2.42)) and increased more than six-fold for APIs (IRR, 2007–11: 6.53 (3.09, 16.21)). Increases occurred in almost every patient subgroup (Figures 2i–l) at 4%–6% per year, with a three-fold higher rate by 2007–2011 for children (IRR: 3.59 (1.82, 7.76) (2j)), and

significant rises in almost all SEER regions (data not shown). Figure 1 illustrates a crossover of MC and NOS rates occurring around 1999.

### Comparison of MC and NOS rates over time

For the period 1992–96, NOS rates were approximately half of MC rates overall (IRR, NOS vs. MC: 0.55 (0.49, 0.61)) and for most patient and tumor characteristics (Supplemental Table 1). For the period 2007–11, NOS rates were approximately double MC rates overall (IRR, NOS vs. MC: 2.14 (1.94, 2.35)) and across study characteristics. The later NOS rates were quite similar to the earlier MC rates overall (IRR, NOS 2007–11 vs. MC 1992–96: 1.19 (1.1, 1.3)), although they were higher for females (IRR: 1.53 (1.33, 1.76)), whites and blacks (IRR: 1.21 (1.09, 1.34), and 1.38 (1.07, 1.78), respectively), and extranodal disease (IRR 5.59 (2.97, 11.69)). The Supplemental Figure illustrates similarities in 2007–11 NOS and 1992–96 MC age-specific rate curves except for AYAs (IRR, NOS 2007–11 vs. MC 1996–96: 1.33 (1.16, 1.54) and over age 80 (IRR: 1.76 (1.26, 2.48)). For combined MC/NOS rates, Table 3 (first column) shows minimal (<1%) annual change overall) but significant increases for females and blacks after 2000, for whites and APIs over the study period, and for AYAs starting in 1998 after a prior decline. Very similar patterns occurred in combined rates also including LD (Table 3, second column). With the addition of NS 9664–9667 (Table 3, third column), trends in combined rates were seen only for persons over age 80, and for localized and regional disease.

### Review of original pathology reports for NOS-coded cases

Among the 165 reviewed pathology reports, 88 (53.3%) contained information providing insight into the choice of the NOS code; these cases were different ( $p < 0.05$ ) than the 77 without such information on disease stage (17.4% vs. 6.4% early stage), biopsy type (39.1% vs. 12.8% excisional), biopsy site (92.0% vs. 80.8% lymph node), facility type (33.3% vs. 20.5% NCI-designated cancer center), and location of final diagnosis (34.5% vs. 11.5% outside consultation). Pathology report text directly justified the NOS classification for 20 cases (12.1%), described biopsy material as insufficient for further subtyping for 21 (12.7%) cases, and described a more specific subtype but without the definitive terminology required by SEER for coding for 14 (8.5%). For 27 cases (16.4%), coders had missed specific subtypes; for five cases (3.0%), they overlooked non-HL diagnoses (four non-Hodgkin lymphomas, one neuroendocrine tumor). Regarding biopsy type, core/FNA biopsies had been used in 121 cases (73.3%) overall and in 20 of the 21 (95.2%) cases described as having inadequate specimens; the only study factor significantly associated with biopsy type overall was stage, with core/FNA biopsies used in the diagnosis of 40.0%, 74.2%, and 85.1% cases with local, regional and distant stage disease, respectively.

## DISCUSSION

In the most recent two decades of SEER data, cHL incidence rates overall were stable until 2007, then showed the first downturn in many years (12). Among cHL subtypes, NS had rates that were unchanged over the first 15 study years before declining, with variation in trends by gender and age; similar patterns and variation for the most common NS subtype (code 9663) are suggestive of a true incidence change. In contrast, rate decreases for MC

and increases for NOS were seen largely irrespective of patient gender, age group, race/ethnicity, tumor stage and site, and SEER registry—a uniformity suggestive of artifactual changes. Growing classification of true MC as NOS over time was suggested by the opposing directions of the MC and NOS incidence trends, the similarity of age-specific incidence rates of NOS for 2007–11 and MC for 1992–96, and the minimal temporal increases in combined MC/NOS rates overall. Further, the uniform declines in the less common subtypes LD and NS codes 9664–9667, and the virtual absence of trends in rates also including these subtypes, support similar misclassification as NOS. Our review of NOS pathology reports provided evidence of likely contributing pathology practices, including prevalent use of non-excisional biopsies and stated insufficiency of biopsy specimens for histologic diagnosis, and of limitations in coding accuracy. For nLP, rate increases over time and across patient subgroups are consistent with the new designation of nLP as a separate disease entity in 1994 (3), although a true incidence rise cannot be ruled out. Together, these findings identify histology-specific HL incidence time trends with both etiologic significance (i.e., rate declines in the main NS category) and practical implications (i.e., misclassification of MC, LD, and NS 9664–9667 as NOS, and inadequate quality control of coding). The former change appears to have impacted overall cHL incidence and should be instructive to HL etiology. The latter changes reveal diminishing utility of the WHO classification system for HL, with nearly 30% of cHL diagnoses not subclassified by 2011.

Prior studies of HL incidence trends reported stable or slightly declining overall rates since the 1990s (12, 21, 39). This pattern, noted also in the first 15 years of our study period (40, 41), contrasts with larger HL rate decreases in earlier periods (42–48). As those latter trends were attributed to improving diagnostic differentiation of HL and non-Hodgkin lymphomas (44, 45), the cHL rate stability documented here may reflect the clearer differentiation among broad lymphoma types since implementation of the 1994 REAL and 2001 WHO classifications. For NS, previous studies reported no recent change in rates overall in the U.S. (12, 21, 39), whereas NS rates rose modestly in Australia through 2006 (20) and significantly in Japan through 2008 (21). For young-adult HL (which mostly comprises NS), several investigations found increasing incidence (48–51); in Australia, NS rates rose 5% annually for 15–24 year olds over the period 1997–2006 (20). However, in more recent SEER data (through 2010), rates for ages 20–44 declined since the mid-2000s, with some gender variation (52), as we also noted. For MC and NOS, our findings of decreasing and increasing rates, respectively, extend previous reports for the U.S. (12, 21) and Australia (20), although they differ from MC rate increases reported for Japan (21).

Trends in histology-specific HL rates could be a consequence of secular changes in risk factors. For the predominant NS category, recent declines could reflect changes in environments fostering early-life social isolation, which has been established to affect HL risk in young adults (53–59). Some of these factors (e.g., family size and birth order) have had decreasing importance to HL risk, likely because of changing prevalences resulting from demographic shifts (54, 60–64). However, preschool attendance has emerged as a protective factor (54). For the AYA birth cohorts in this study period, the rising percentages of children under age 5 in daycare or preschool (i.e., 8%, 15%, 20%, 30%, 31%, 28%, and 35% in 1965, 1977, 1982, 1984–85, 1988, 1991 and 1993, respectively (65)) are consistent with the observed declines in AYA NS rates. However, these attendance data do not speak to the

gender differences in NS rate declines, which are consistent with well described but little understood gender differences in young-adult HL incidence, including cohort effects (52).

For MC, which is associated with lower socioeconomic status (23, 24), a general rise in the standard of living could have contributed to the rate decline, although SES changes in the U.S. over the study period have not been substantial. Changes in HIV infection prevalence also could have affected observed rates (25, 66). Since 1992, the incidence of new HIV infections in the U.S. increased and then stabilized (67); highly active anti-retroviral therapies introduced in the mid-1990s may have lessened HL risk, although their impact remains unclear (25). However, the occurrence of MC rate decreases across gender and age groups, and the low proportion of HIV-positive MC cases (10% of males (25)), suggest that the observed MC trends are not largely attributable to HIV infection. In SEER data restricted to California (38% of all study cases), overall MC rates (n=7,485) decreased whether the 515 cases with HIV/AIDS (68) were included (APC=-4.2 (-5.3, -3.1) for 1992-2011) or excluded (APC =-4.1 (-5.2, -3.1) for 1992-2011). Long-standing decreases in cigarette smoking prevalence (69) could have contributed to the observed rate decreases (28). MC rates also could be declining due to increasing westernization of immigrants, in whom MC risk is elevated (24, 70). However, we observed no differences in MC trends between whites and Hispanics or APIs, populations with large immigrant subgroups (70, 71). Further, in California data (70), MC rates declined between 1988-92 and 2000-04 similarly for whites, US-born Hispanics, and foreign-born Hispanics (data not shown).

Thus, artifact likely underlies the trends noted here, reflecting changes in diagnostic and/or classification practice. Changes in diagnostic practice have occurred with the advent of core needle biopsies and FNA in place of excisional biopsies (72). While less invasive, these new methods yield a smaller quantity and often lower quality of tumor tissue, specifically the tissue preserving tumor architecture; indeed, our review of NOS pathology reports found specimen inadequacy for subtyping mentioned in 12% of cases. This consequence of core/FNA biopsies could result in poorer diagnostic specificity for HL (73), given the difficulties of diagnosing HL with these methods (37). Diagnostic specificity due to lower quality specimens would be more likely to occur with MC than NS, since characteristic morphology of the latter often is retained in the needle biopsy. Gradual adoption of the new biopsy methods is consistent with our findings of similarities in later NOS to earlier MC rates, presumably as the decreasing ability to diagnose MC (and LD (74)) led to greater use of the NOS classification. A similar explanation may hold for cellular phase NS (code 9664, which also was excluded from the WHO classification in 2008), whereas the drop-off in the use of NS grade subtypes (codes 9665, 9667) likely reflects its lack of clinical relevance with modern chemotherapy (35, 36). Changes in classification practice also could have contributed to the trends observed here, if the WHO classification has been increasingly interpreted as requiring only distinction between cHL and nLP, given clinical requirements (72). Our finding that nearly half of the reviewed NOS diagnoses were recorded without further comment, while not directly addressing the pathologists' rationale, is consistent with such a trend.

This study used a large database that permitted detailed evaluation of histology-specific rates, and whose high-quality population-based data with standardized coding yielded



reliable findings generalizable to similar populations. Our pathology report review provided preliminary insights into diagnostic and classification practices for NOS. However, we were unable to evaluate the impact on histology rate trends of facility type, a factor previously associated with diagnostic accuracy of lymphomas (75), or of facility type and case volume, factors related to the specificity of histologic typing for other cancers (76). As our NOS quality-control review occurred in a single regional registry for a recent time period, it cannot speak to more widespread diagnostic practices or trends over time.

Diminishing specificity of histologic subtyping for cHL has important implications. For epidemiology, it renders histology-specific incidence rates difficult to interpret and confounds secular trends. Despite lacking a biological definition, NOS must be included as a subtype in HL research, as it is now the second most common cHL category. The potential to HL etiology of subtype differences in gene expression profiling (6) and transcriptional analyses of HL malignant cells (8) may be reduced. Finally, although subtypes are not included in clinical decision-making, their varying survival patterns suggest that more tailored therapies might be reconsidered (9, 10, 15, 77).

For all these purposes, accurate histologic subtyping is needed, which requires use of excisional biopsies as indicated and comprehensive central registry quality control. Less invasive biopsy techniques have patient benefits, and should be used for screening (i.e., to rule out malignancy), follow-up biopsies, deep lesions, or when an open biopsy is clinically contraindicated (e.g., by age, comorbidity, etc.). However, in other situations, excisional biopsies should be used as the first choice for the initial diagnosis, in accordance with National Comprehensive Cancer Network guidelines (78). Our finding of NOS coding in error in a California registry may reflect state budget-driven reductions in central registry quality control practices and indicates that enhanced quality control would be of benefit, at least for HL.

In a large, population-based series of HL cases diagnosed over 20 recent years, we have found that histologic subtyping is diminishing. This pattern, which runs counter to the well-established heterogeneity of HL by histologic subtype (79), has an important impact on future HL research, particularly surveillance and epidemiologic studies, and investigations of treatments targeted to reduce survival disparities across subtypes. Adherence to current biopsy best practices for HL, together with improved quality control of lymphoma subtype coding, may help remediate this troubling trend.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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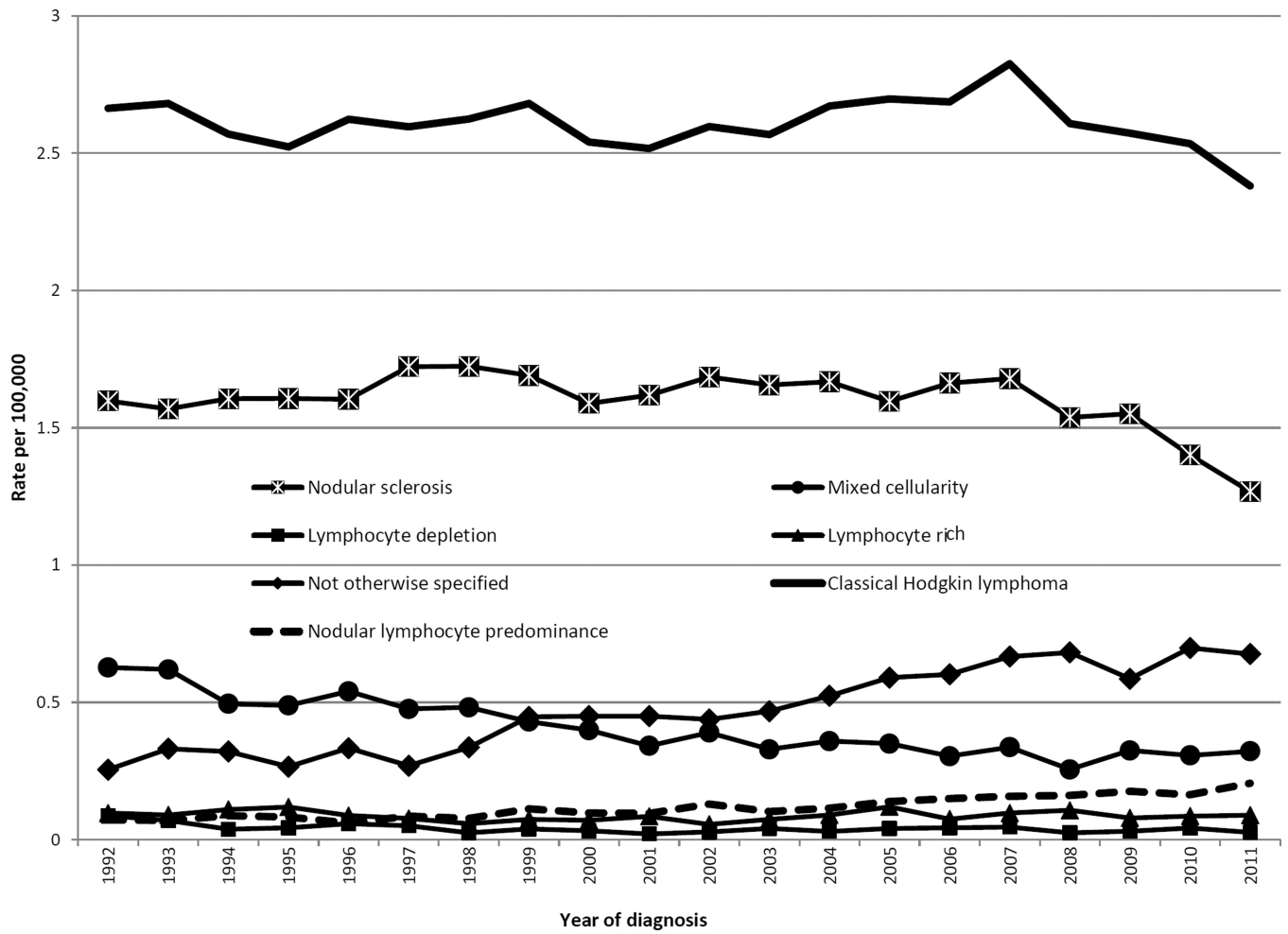
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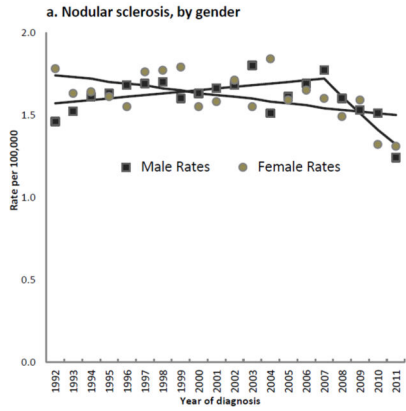
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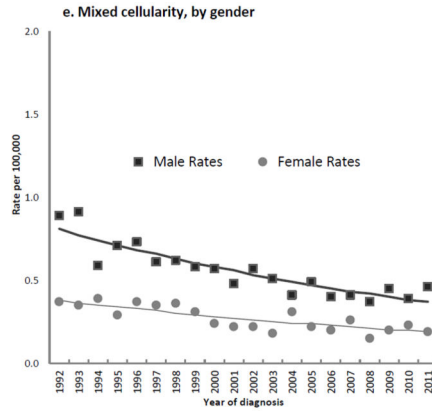


**Figure 1.** Annual age-adjusted incidence rates of Hodgkin lymphoma by histologic subtype and year of diagnosis, 1992–2011, SEER (13 registries)

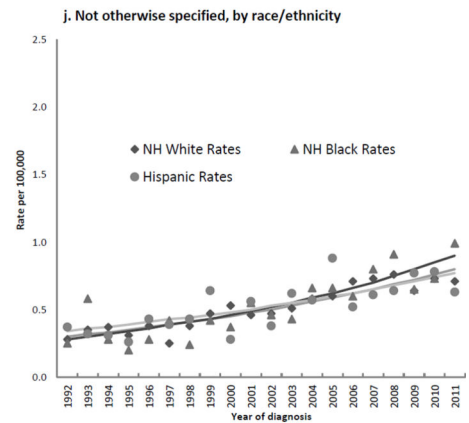
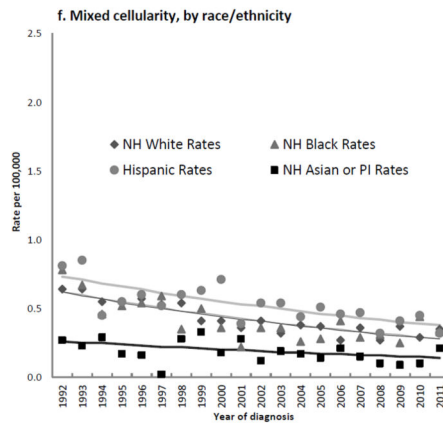
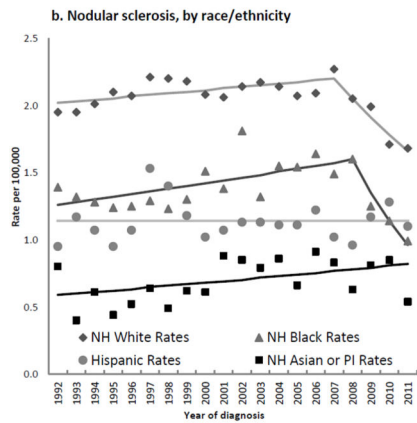
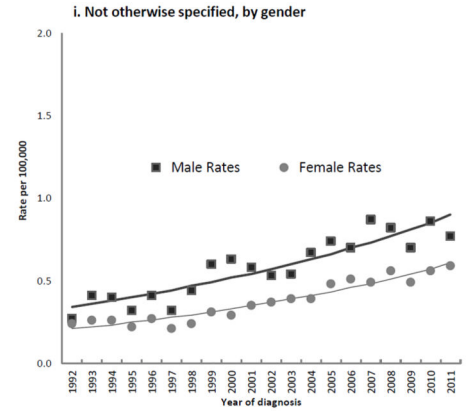
**Nodular sclerosis**



**Mixed cellularity**



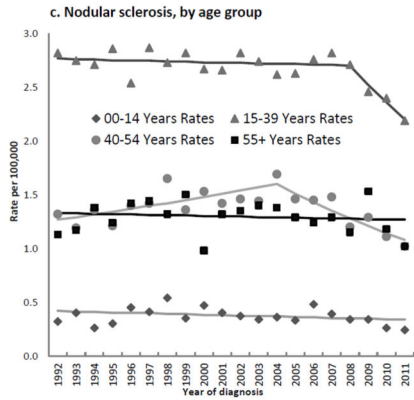
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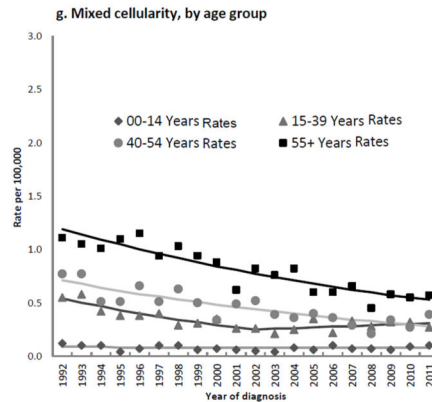
\* Joinpoint cannot process records with missing dependent variable values



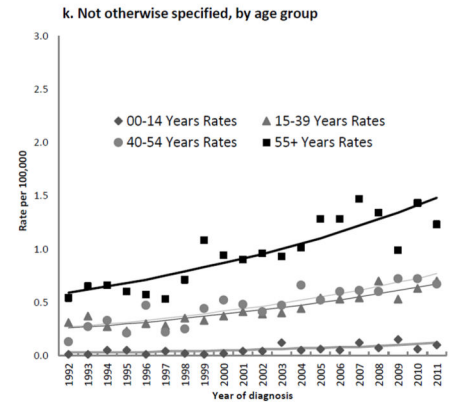
**Nodular sclerosis**



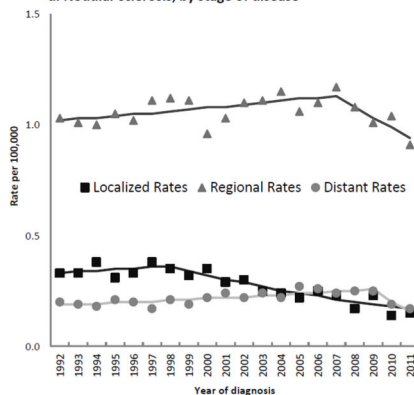
**Mixed cellularity**



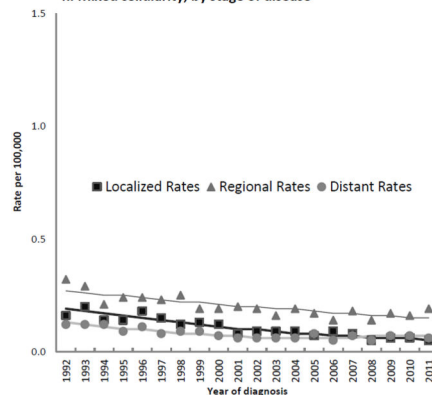
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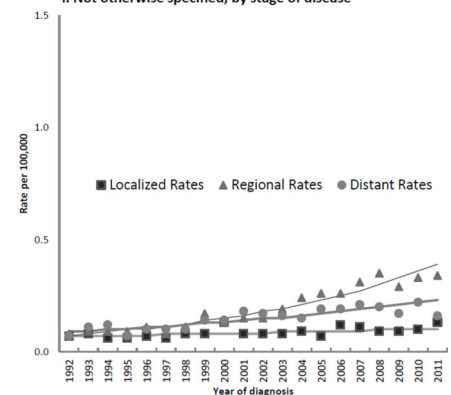
**d. Nodular sclerosis, by stage of disease**



**h. Mixed cellularity, by stage of disease**



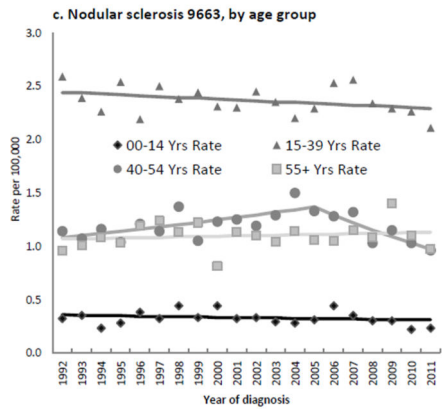
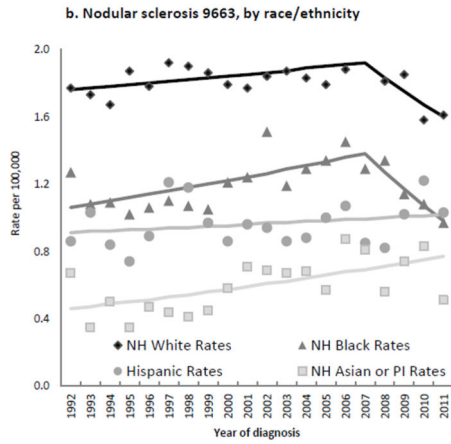
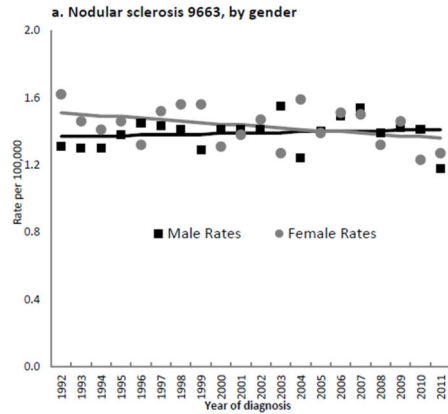
**i. Not otherwise specified, by stage of disease**



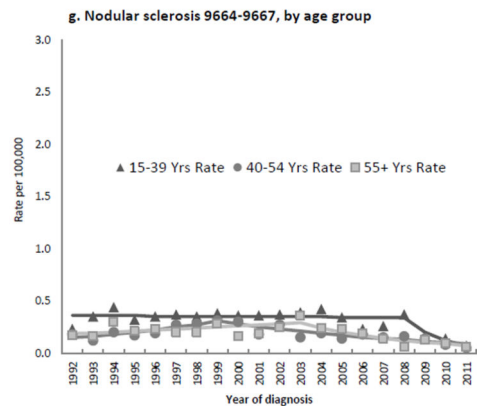
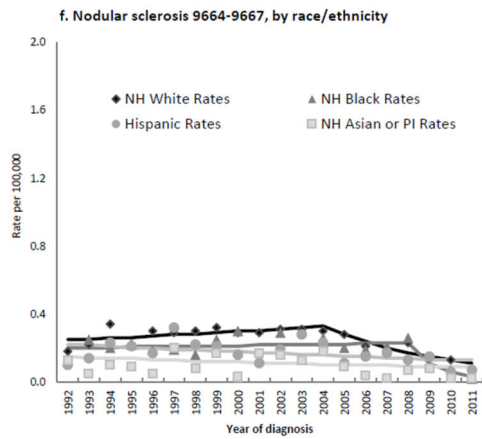
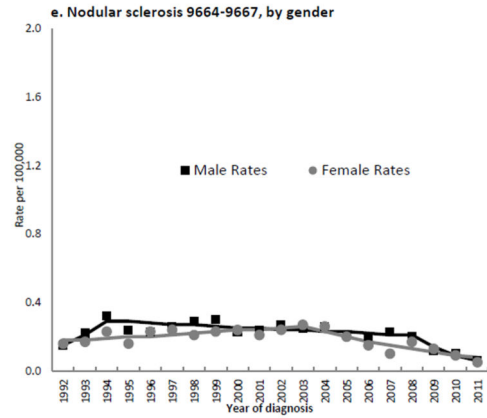
\* Joinpoint cannot process records with missing dependent variable values

**Figure 2.** Annual age-adjusted incidence rates\*, and Joinpoint trend lines, of selected Hodgkin lymphoma histologic subtypes by patient and tumor characteristics, 1992–2011, SEER (13 registries)

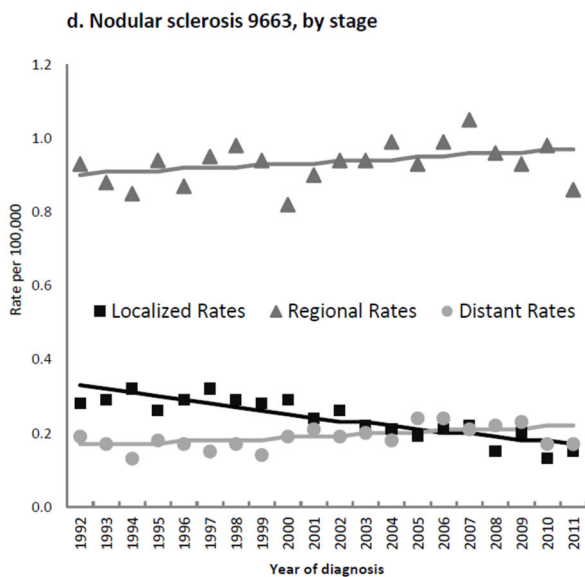
**Nodular sclerosis 9663‡**



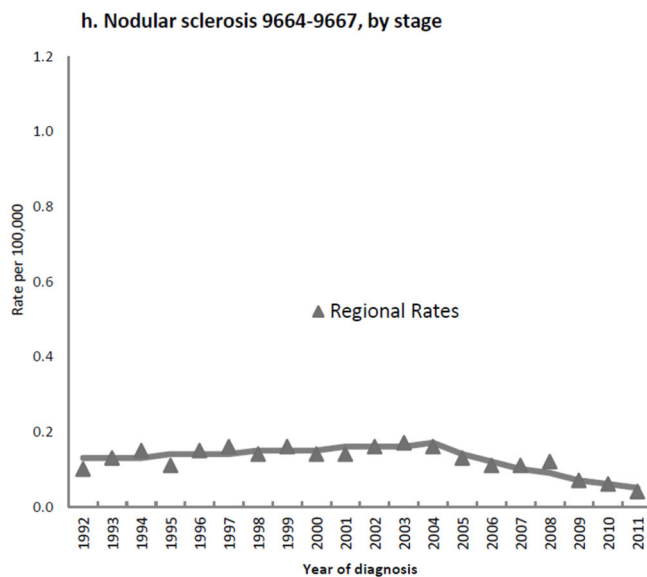
**Nodular sclerosis 9664-9667‡**



**Nodular sclerosis 9663‡**



**Nodular sclerosis 9664-9667‡**



‡ ICD-O-3 codes; \* Joinpoint cannot process records with missing dependent variable values.

**Figure 3.**  
Annual age-adjusted incidence rates\*, and Joinpoint trend lines, of nodular sclerosis Hodgkin lymphoma subtypes by patient and tumor characteristics, 1992–2011, SEER (13 registries)

Joinpoint average percent change (APC)\* and 95% confidence intervals (CI) for Hodgkin lymphoma incidence rates, by histologic subtype and patient and tumor characteristics, 1992–2011, SEER (13 registries)

Table 1

Overall	Classical Hodgkin lymphoma																	
	Nodular sclerososis			Mixed cellularity			Lymphocyte depletion			Lymphocyte rich			Not otherwise specified			Nodular lymphocyte predominance		
	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)		
N=20,437	N=12,722			N=3,069			N=303			N=673			N=3670			N=935		
1992–2002	-0.3 (-0.8, 0.3)	1992–2007	0.2 (-0.2, 0.6)	1992–2011	-4 (-4.7, -3.3)	1992–2011	-3.6 (-5.6, -1.5)	1992–2011	0.1 (-1.5, 1.8)	1992–2011	5.3 (4.5, 6.2)	1992–2011	5.9 (5.1, 6.8)	1992–2011	5.3 (4.5, 6.2)	1992–2011	5.9 (5.1, 6.8)	
2002–2007	1.5 (-0.5, 3.6)	2007–2011	-5.9 (-8.8, -2.9)															
2007–2011	-3.6 (-5.6, -1.5)																	
<b>TOTAL</b>																		
1992–2011	-0.1 (-0.5, 0.3)	1992–2007	0.6 (0.1, 1.3)	1992–2011	-4.1 (-5.1, -3.2)	1992–2011	-5.7 (-8.3, -3)	1992–2011	-1.7 (-3.5, 0.2)	1992–2011	5.2 (3.9, 6.5)	1992–2011	6.2 (5.2, 7.2)	1992–2011	5.2 (3.9, 6.5)	1992–2011	6.2 (5.2, 7.2)	
2007–2011	-6.4 (-11, -1.5)																	
1992–2011	-0.1 (-0.6, 0.4)	1992–2011	-0.8 (-1.4, -0.2)	1992–2011	-3.6 (-4.9, -2.3)	1992–2011	-2.4 (-0.2, 5.2)	1992–2011	2.4 (-0.2, 5.2)	1992–2011	5.8 (4.9, 6.7)	1992–2011	5.0 (2.9, 7.2)	1992–2011	5.8 (4.9, 6.7)	1992–2011	5.0 (2.9, 7.2)	
<b>Race/Ethnicity</b>																		
1992–2004	0.1 (-0.3, 0.5)	1992–2007	0.6 (0.1, 1.1)	1992–2011	-4.1 (-5.1, -3.2)	1992–2011	-3.5 (-6, -0.9)	1992–2011	-6.5 (-13.5, 1.1)	1992–2011	5.3 (4.2, 6.4)	1992–2011	6.5 (5.3, 7.8)	1992–2011	5.3 (4.2, 6.4)	1992–2011	6.5 (5.3, 7.8)	
2004–2007	2.7 (-1.0, 9.9)	2007–2011	-6.7 (-10.2, -3.2)															
2007–2011	-4.7 (-6.8, -2.5)																	
1992–2011	0.6 (-0.2, 1.5)	1992–2008	1.5 (0.5, 2.6)	1992–2011	-4.1 (-5.9, -2.4)	1992–2011	-15.6 (-27.2, -2.2)	1992–2011	1.8 (-0.1, 3.6)	1992–2011	6.2 (4.2, 8.3)	1992–2011	5.8 (3.7, 7.8)	1992–2011	6.2 (4.2, 8.3)	1992–2011	5.8 (3.7, 7.8)	
2008–2011	-15.6 (-27.2, -2.2)																	
1992–2011	0.1 (-0.7, 0.9)	1992–2011	0 (-1, 1)	1992–2011	-3.4 (-4.8, -2.1)	1992–2011	1.8 (-2.2, 6)	1992–2011	1.8 (-2.2, 6)	1992–2011	4.4 (2.4, 6.4)	1992–2011	4.4 (2.4, 6.4)	1992–2011	4.4 (2.4, 6.4)	1992–2011	4.4 (2.4, 6.4)	
Hispanic	1992–2011	1.8 (0.5, 3.1)	1992–2011	1.7 (-0.1, 3.6)	1992–2011	-3.1 (-6.1, -0.1)												
API	1992–2011	1.8 (0.5, 3.1)	1992–2011	1.7 (-0.1, 3.6)	1992–2011	-3.1 (-6.1, -0.1)												
AI/AN																		
Unknown																		
<b>Age group (10 years)</b>																		
00–09 years	1992–2011	0.6 (-0.9, 2.0)	1992–2011	-0.7 (-4.0, 2.8)	1992–2011	0.5 (-2.1, 3.1)												

	Classical Hodgkin lymphoma																	
	Nodular lymphocyte predominance			Lymphocyte rich			Lymphocyte depletion			Not otherwise specified								
	Overall	N=20437	N=12722	Mixed cellularity	N=3069	N=303	N=673	N=3670	N=935	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	
10-19 years	1992-1995	-8.2 (-18.1, 2.9)	1992-2011	-0.8 (-1.8, 0.3)	1992-2011	-4.7 (-7, -2.4)	1992-2011	0.7 (-2.4, 3.9)	1992-2011	6.7 (4.6, 8.9)	1992-2011	6.3 (2.7, 10.1)	1992-1998	-3 (-5.9, 0)	1992-2011	-0.7 (-1.3, -0.1)	1992-1999	-11 (-17.7, -3.7)
	1995-1998	9.7 (-11.6, 36.1)											1998-2001	0.8 (-0.2, 1.8)	1999-2011	2.2 (-2, 6.6)	1999-2011	2.2 (-2, 6.6)
	1998-2001	-9.8 (-27.7, 12.6)											2001-2011	<b>1.9 (0.1, 3.6)</b>				
20-29 years	1992-2008	0.5 (-0.1, 1)	1992-2003	2 (0.6, 3.4)	1992-2011	-3.3 (-4.9, -1.8)	1992-2011	0.7 (-2.4, 3.9)	1992-2011	4.3 (2.7, 5.9)	1992-2011	2.8 (0.5, 5.2)	1992-2008	0.5 (-0.1, 1)	1992-2011	-0.7 (-1.3, -0.1)	1992-1999	-11 (-17.7, -3.7)
	2008-2011	<b>-8.4 (-14.9, -1.9)</b>	2003-2011	<b>-4.6 (-7, -2.2)</b>	2006-2011	<b>-8.7 (-14.3, -2.7)</b>	1992-2011	-3 (-6.8, 0.9)	1992-2011	5.0 (3.0, 7.0)	1992-2011	6.5 (3.5, 9.5)	1998-2011	0.8 (-0.2, 1.8)	1999-2011	2.2 (-2, 6.6)	1999-2011	2.2 (-2, 6.6)
30-39 years	1992-2011	-0.7 (-1.6, 0.3)	1992-2011	-1.6 (-3, -0.3)	1992-2011	-5.5 (-7.3, -3.7)	1992-2011	2 (-1.3, 5.4)	1992-2011	6.2 (4.2, 8.2)	1992-2011	6.2 (4.2, 8.2)	1992-2011	-0.7 (-1.6, 0.3)	1992-2011	-0.7 (-1.6, 0.3)	1992-2011	0.8 (-1.2, 0.6)
40-49 years	1992-2011	-0.7 (-1.6, 0.3)	1992-2011	-3 (-4.8, -1)	1992-2011	-4.3 (-6.2, -2.3)	1992-2011	1.3 (-3.1, 5.8)	1992-2011	3.8 (1.5, 6.0)	1992-2011	7.6 (3.6, 11.7)	1992-2011	-0.7 (-1.6, 0.3)	1992-2011	-0.7 (-1.6, 0.3)	1992-2011	0.8 (-1.2, 0.6)
50-59 years	1992-2011	0.2 (-0.5, 0.9)	1992-2006	1.9 (0.6, 3.3)	1992-2011	-4 (-5.7, -2.2)	1992-2011	-3 (-4.8, -1)	1992-2011	4.1 (0.7, 7.7)	1992-2011	5.2 (3.0, 7.5)	1992-2011	0.2 (-0.7, 1.1)	1992-2011	0.8 (-1.2, 0.6)	1992-2011	0.8 (-1.2, 0.6)
60-69 years	1992-2011	0.2 (-0.7, 1.1)	1992-2011	0.6 (-1.1, 2.3)	1992-2011	-5 (-6.7, -3.3)	1992-2011	-1.8 (-3.7, 0)	1992-2011	5.7 (3.6, 7.9)	1992-2011	5.7 (3.6, 7.9)	1992-2011	0.2 (-0.7, 1.1)	1992-2011	0.8 (-1.2, 0.6)	1992-2011	0.8 (-1.2, 0.6)
70-79 years	1992-2011	1.9 (0.7, 3.1)	1992-2011	0.6 (-1.1, 2.3)	1992-2011	-1.8 (-3.7, 0)	1992-2011	-1.8 (-3.7, 0)	1992-2011	5.7 (3.6, 7.9)	1992-2011	5.7 (3.6, 7.9)	1992-2011	1.9 (0.7, 3.1)	1992-2011	1.9 (0.6, 3.3)	1992-2004	1.9 (0.6, 3.3)
80+ years	1992-2011	0.2 (-0.7, 1.1)	1992-2011	0.6 (-1.1, 2.3)	1992-2011	-1.8 (-3.7, 0)	1992-2011	-1.8 (-3.7, 0)	1992-2011	5.7 (3.6, 7.9)	1992-2011	5.7 (3.6, 7.9)	1992-2011	0.2 (-0.7, 1.1)	1992-2011	0.8 (-1.2, 0.6)	1992-2011	0.8 (-1.2, 0.6)
<b>Age groups</b>																		
00-14 years	1992-2011	0 (-1.1, 1.1)	1992-2011	-1.1 (-2.8, 0.7)	1992-2011	-0.7 (-3, 1.7)	1992-2011	-0.7 (-3, 1.7)	1992-2011	8.5 (3.8, 13.3)	1992-2011	8.5 (3.8, 13.3)	1992-2011	0 (-1.1, 1.1)	1992-2011	-1.1 (-2.8, 0.7)	1992-2011	-1.1 (-2.8, 0.7)
15-39 years	1992-2011	-0.3 (-0.6, 0.1)	1992-2008	-0.1 (-0.6, 0.3)	1992-2002	-7.4 (-10.2, -4.5)	1992-2011	-0.7 (-3, 1.7)	1992-2011	-2.1 (-4.5, 0.3)	1992-2011	3.7 (2.2, 5.3)	1992-2011	-0.3 (-0.6, 0.1)	1992-2008	-0.1 (-0.6, 0.3)	1992-2002	-7.4 (-10.2, -4.5)
	2008-2011	<b>-6.7 (-11.9, -1.2)</b>	2002-2011	2.4 (-2.2, 7.1)	2002-2011	2.4 (-2.2, 7.1)	1992-2011	-0.6 (-3.6, 2.5)	1992-2011	5.7 (3.9, 7.6)	1992-2011	6.5 (4.4, 8.6)	2008-2011	<b>-6.7 (-11.9, -1.2)</b>	2002-2011	2.4 (-2.2, 7.1)	2002-2011	2.4 (-2.2, 7.1)
40-54 years	1992-2011	-0.1 (-0.7, 0.6)	1992-2004	1.9 (0.6, 3.3)	1992-2011	-4.7 (-6.1, -3.3)	1992-2011	-0.6 (-3.6, 2.5)	1992-2011	5.7 (3.9, 7.6)	1992-2011	6.5 (4.4, 8.6)	1992-2011	-0.1 (-0.7, 0.6)	1992-2004	1.9 (0.6, 3.3)	1992-2011	-4.7 (-6.1, -3.3)
	2004-2011	<b>-5.4 (-8.3, -2.6)</b>	2004-2011	<b>-5.4 (-8.3, -2.6)</b>	2004-2011	<b>-5.4 (-8.3, -2.6)</b>	1992-2011	-5.8 (-8.6, -2.8)	1992-2011	5.0 (3.5, 6.4)	1992-2011	7.2 (4.7, 9.8)	2004-2011	<b>-5.4 (-8.3, -2.6)</b>	2004-2011	<b>-5.4 (-8.3, -2.6)</b>	2004-2011	<b>-5.4 (-8.3, -2.6)</b>
55+ years	1992-2011	0.1 (-0.4, 0.6)	1992-2011	-0.3 (-1.2, 0.7)	1992-2011	-4.2 (-5.1, -3.3)	1992-2011	-5.8 (-8.6, -2.8)	1992-2011	5.0 (3.5, 6.4)	1992-2011	7.2 (4.7, 9.8)	1992-2011	0.1 (-0.4, 0.6)	1992-2011	-0.3 (-1.2, 0.7)	1992-2011	-4.2 (-5.1, -3.3)
	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)	2001-2004	31 (-26.9, 134.5)
	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>	2004-2011	<b>-5.8 (-11, -0.3)</b>
<b>Stage</b>																		

	Classical Hodgkin lymphoma																		
	Nodular sclerosi			Mixed cellularity			Lymphocyte depletion			Lymphocyte rich			Not otherwise specified			Nodular lymphocyte predominance			
	Interval (yrs)	APC (95% CI)	N	Interval (yrs)	APC (95% CI)	N	Interval (yrs)	APC (95% CI)	N	Interval (yrs)	APC (95% CI)	N	Interval (yrs)	APC (95% CI)	N	Interval (yrs)	APC (95% CI)	N	
<b>Overall</b>			<b>N=20,437</b>			<b>N=3,069</b>			<b>N=303</b>			<b>N=673</b>			<b>N=3,670</b>			<b>N=935</b>	
Localized	1992-2011	-3.2 (-3.9, -2.5)	1992-1998	1.2 (-3.9, 6.6)	1992-2011	-6.5 (-7.7, -5.4)	1992-2011	-3.4 (-4.1, -2.1)	1992-2011	0.9 (-1.2, 8)	1992-2011	-3.4 (-5, -1.8)	1992-2011	2.3 (0.9, 3.8)	1992-2011	2.3 (0.9, 3.8)	1992-2011	2.8 (1.8, 3.9)	
			1998-2011	-5.6 (-7.4, -3.8)															
Regional	1992-2011	0.7 (0.2, 1.1)	1992-2007	0.7 (0.1, 1.3)	1992-2011	-3.1 (-4.1, -2.1)	1992-2011	-3.1 (-4.1, -2.1)	1992-2011	0.9 (-1.2, 8)	1992-2011	0.9 (-1.2, 8)	1992-2011	9.2 (7.7, 10.7)	1992-2011	9.2 (7.7, 10.7)	1992-2011	8.4 (6.9, 9.8)	
			2007-2011	-4.4 (-8.7, 0.1)															
Distant	1992-2009	1.7 (0.9, 2.5)	1992-2009	1.9 (1.1, 2.7)	1992-2002	-6.9 (-9.9, -3.9)	1992-2011	-6.9 (-9.9, -3.9)	1992-2011	1992-2011	5.0 (3.3, 6.8)	1992-2011	5.0 (3.3, 6.8)	1992-2011	5.0 (3.3, 6.8)	1992-2011	5.0 (3.3, 6.8)	1992-2011	5.0 (3.3, 6.8)
	2009-2011	-10 (-27.3, 11.5)	2009-2011	-20.4 (-38.2, 2.7)	2002-2011	0.7 (-2.9, 4.4)	2002-2011	0.7 (-2.9, 4.4)	2002-2011	2002-2011	0.7 (-2.9, 4.4)	2002-2011	0.7 (-2.9, 4.4)	2002-2011	0.7 (-2.9, 4.4)	2002-2011	0.7 (-2.9, 4.4)	2002-2011	0.7 (-2.9, 4.4)
NA and unstaged	1992-2011	-0.6 (-1.9, 0.8)	1992-2011	0.2 (-1.9, 2.3)	1992-2011	0.2 (-1.9, 2.3)	1992-2011	0.2 (-1.9, 2.3)	1992-2011	1992-2011	-0.5 (-2.4, 1.4)	1992-2011	-0.5 (-2.4, 1.4)	1992-2011	-0.5 (-2.4, 1.4)	1992-2011	-0.5 (-2.4, 1.4)	1992-2011	-0.5 (-2.4, 1.4)
<b>Tumor site</b>																			
Nodal	1992-2003	-0.3 (-0.7, 0.1)	1992-2007	0.2 (-0.2, 0.6)	1992-2011	-4.1 (-4.9, -3.4)	1992-2011	-4.3 (-6.3, -2.1)	1992-2011	-0.2 (-1.9, 1.5)	1992-2011	-0.2 (-1.9, 1.5)	1992-2011	5.2 (4.2, 6.2)	1992-2011	5.2 (4.2, 6.2)	1992-2011	6.0 (5.0, 7.0)	
	2003-2007	1.8 (-1.2, 5)	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	-6.2 (-9.1, -3.1)	2007-2011	-6.2 (-9.1, -3.1)
Extranodal	2007-2011	-3.7 (-5.6, -1.8)	1992-2011	2.3 (0.1, 4.5)	1992-2011	2.3 (0.1, 4.5)	1992-2011	2.3 (0.1, 4.5)	1992-2011	1992-2011	2.3 (0.1, 4.5)	1992-2011	2.3 (0.1, 4.5)	1992-2011	2.3 (0.1, 4.5)	1992-2011	2.3 (0.1, 4.5)	1992-2011	2.3 (0.1, 4.5)
<b>Registry</b>																			
Connecticut	1992-2011	-0.6 (-1.2, 0)	1992-2003	2.2 (0.5, 3.9)	1992-2001	-12.8 (-18.3, -6.9)	1992-2011	-12.8 (-18.3, -6.9)	1992-2011	-1.1 (-5.2, 3.2)	1992-2011	-1.1 (-5.2, 3.2)	1992-2011	5.0 (2.8, 7.2)	1992-2011	5.0 (2.8, 7.2)	1992-2011	5.0 (2.8, 7.2)	
			2003-2011	-7.1 (-9.8, -4.3)	2001-2011	3.0 (-3.9, 10.5)	2001-2011	3.0 (-3.9, 10.5)	2001-2011	2001-2011	3.0 (-3.9, 10.5)	2001-2011	3.0 (-3.9, 10.5)	2001-2011	3.0 (-3.9, 10.5)	2001-2011	3.0 (-3.9, 10.5)	2001-2011	3.0 (-3.9, 10.5)
Detroit	1992-2011	-0.3 (-1.2, 0.6)	1992-2008	0.7 (-0.5, 2)	1992-2011	-2.7 (-4.5, -0.9)	1992-2011	-2.7 (-4.5, -0.9)	1992-2011	0 (-3.2, 3.4)	1992-2011	0 (-3.2, 3.4)	1992-2011	2.6 (0.7, 4.7)	1992-2011	2.6 (0.7, 4.7)	1992-2011	6.4 (5.0, 10.0)	
			2008-2011	-17.0 (-30.8, -0.4)	2008-2011	-17.0 (-30.8, -0.4)	2008-2011	-17.0 (-30.8, -0.4)	2008-2011	2008-2011	-17.0 (-30.8, -0.4)	2008-2011	-17.0 (-30.8, -0.4)	2008-2011	-17.0 (-30.8, -0.4)	2008-2011	-17.0 (-30.8, -0.4)	2008-2011	-17.0 (-30.8, -0.4)
Hawaii	1992-2011	1.3 (-0.5, 3.3)	1992-2011	2.0 (-0.4, 4.4)	1992-2011	2.0 (-0.4, 4.4)	1992-2011	2.0 (-0.4, 4.4)	1992-2011	1992-2011	5.5 (1.7, 9.4)	1992-2011	5.5 (1.7, 9.4)	1992-2011	5.5 (1.7, 9.4)	1992-2011	5.5 (1.7, 9.4)	1992-2011	5.5 (1.7, 9.4)
Iowa	1992-2011	0.1 (-0.7, 1)	1992-2011	-0.4 (-1.4, 0.5)	1992-2011	-2.1 (-4.4, 0.3)	1992-2011	-2.1 (-4.4, 0.3)	1992-2011	1992-2011	6.9 (3.8, 10.2)	1992-2011	6.9 (3.8, 10.2)	1992-2011	6.9 (3.8, 10.2)	1992-2011	6.9 (3.8, 10.2)	1992-2011	6.9 (3.8, 10.2)
New Mexico	1992-2011	-0.6 (-1.8, 0.5)	1992-2011	-3.9 (-5.7, -2.0)	1992-2011	1.3 (-3.5, 6.2)	1992-2011	1.3 (-3.5, 6.2)	1992-2011	1992-2011	4.5 (1.0, 8.1)	1992-2011	4.5 (1.0, 8.1)	1992-2011	4.5 (1.0, 8.1)	1992-2011	4.5 (1.0, 8.1)	1992-2011	4.5 (1.0, 8.1)
Seattle	1992-2011	-0.1 (-0.7, 0.5)	1992-2009	1.0 (-0.1, 2.1)	1992-2011	-4.3 (-6.2, -2.3)	1992-2011	-4.3 (-6.2, -2.3)	1992-2011	-1.4 (-4.6, 2.0)	1992-2011	-1.4 (-4.6, 2.0)	1992-2011	5.3 (3.7, 6.9)	1992-2011	5.3 (3.7, 6.9)	1992-2011	4.9 (2.6, 7.2)	
			2009-2011	-20.9 (-43.9, 11.6)	2009-2011	-20.9 (-43.9, 11.6)	2009-2011	-20.9 (-43.9, 11.6)	2009-2011	2009-2011	-20.9 (-43.9, 11.6)	2009-2011	-20.9 (-43.9, 11.6)	2009-2011	-20.9 (-43.9, 11.6)	2009-2011	-20.9 (-43.9, 11.6)	2009-2011	-20.9 (-43.9, 11.6)
Utah	1992-2011	0.7 (-0.3, 1.6)	1992-2011	0.9 (-0.4, 2.2)	1992-2011	-2.1 (-6.3, 2.3)	1992-2011	-2.1 (-6.3, 2.3)	1992-2011	1992-2011	3.3 (-0.4, 7.2)	1992-2011	3.3 (-0.4, 7.2)	1992-2011	3.3 (-0.4, 7.2)	1992-2011	3.3 (-0.4, 7.2)	1992-2011	3.3 (-0.4, 7.2)
Atlanta	1992-2011	-0.2 (-1.4, 0.9)	1992-2011	-0.7 (-2.1, 0.7)	1992-2011	-4.6 (-7, -2.2)	1992-2011	-4.6 (-7, -2.2)	1992-2011	1992-2011	4.4 (1.2, 7.7)	1992-2011	4.4 (1.2, 7.7)	1992-2011	4.4 (1.2, 7.7)	1992-2011	4.4 (1.2, 7.7)	1992-2011	4.4 (1.2, 7.7)

		Classical Hodgkin lymphoma																	
		Nodular lymphocyte predominance			Lymphocyte rich			Lymphocyte depletion			Not otherwise specified								
		N=12722			N=3069			N=303			N=673			N=3670			N=935		
Overall	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	
	1992-2011	0.3 (-0.6, 1.1)	1992-2011	-1.3 (-2.5, -0.1)	1992-1999	4.1 (-3.1, 11.8)	1992-2011	-6.6 (-9.6, -3.5)	1992-2011	1.0 (-1.7, 3.8)	1992-2011	5.2 (3.5, 6.9)	1992-2011	7.7 (5.1, 10.3)	1992-2011	4.6 (2.5, 6.8)	1992-2011	3.4 (1.0, 5.8)	
San Francisco-Oakland	1992-2011	0.3 (-0.6, 1.1)	1992-2011	-1.3 (-2.5, -0.1)	1999-2002	-40.5 (-71.9, -25.9)	1992-2011	-5.8 (-8.6, -2.9)	1992-2011	1.0 (-1.7, 3.8)	1992-2011	5.2 (3.5, 6.9)	1992-2011	7.7 (5.1, 10.3)	1992-2011	4.6 (2.5, 6.8)	1992-2011	3.4 (1.0, 5.8)	
				2002-2007	27.4 (1.1, 60.5)														
				2007-2011	-21.7 (-38.4, -0.5)														
San Jose-Monterey	1992-2011	0.1 (-0.9, 1.1)	1992-2011	-0.5 (-2.1, 1.2)	1992-2011	-5.8 (-8.6, -2.9)	1992-2011	-5.8 (-8.6, -2.9)	1992-2011	1.0 (-1.7, 3.8)	1992-2011	5.2 (3.5, 6.9)	1992-2011	7.7 (5.1, 10.3)	1992-2011	4.6 (2.5, 6.8)	1992-2011	3.4 (1.0, 5.8)	
Los Angeles	1992-2011	-0.1 (-0.7, 0.5)	1992-2011	-0.1 (-0.7, 0.6)	1992-2011	-3.5 (-4.7, -2.2)	1992-2011	-6.6 (-9.6, -3.5)	1992-2011	1.0 (-1.7, 3.8)	1992-2011	5.2 (3.5, 6.9)	1992-2011	7.7 (5.1, 10.3)	1992-2011	4.6 (2.5, 6.8)	1992-2011	3.4 (1.0, 5.8)	
Alaska Natives																			
Rural Georgia																			

\* Joinpoint cannot process records when a dependent variable has a value of 0.

**Table 2**

Joinpoint average percent change (APC)\* and 95% confidence intervals (CI) for nodular sclerosis Hodgkin lymphoma incidence rates, by subtype and patient and tumor characteristics, 1992–2011, SEER (13 registries)

Nodular sclerosis				
Not otherwise specified (9663 <sup>‡</sup> )		Cellular phase, Grades 1 and 2 (9664–9667 <sup>‡</sup> )		
N= 11,135		N= 1,587		
	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
<b>TOTAL</b>				
	1992–2009	0.2 (–0.2, 0.6)	1992–2004	2.1 (–0.8, 5)
	2009–2011	–8 (–18.1, 3.3)	2004–2011	<b>–15 (–22.1, –7.2)</b>
<b>Sex</b>				
Male	1992–2011	0.2 (–0.4, 0.7)	1992–1994	38 (–6.6, 103.9)
			1994–2008	<b>–2.4 (–4.2, –0.7)</b>
			2008–2011	<b>–34.1 (–49.9, –13.3)</b>
Female	1992–2011	–0.6 (–1.2, 0.1)	1992–2003	<b>3.6 (0.4, 6.9)</b>
			2003–2011	<b>–13.6 (–19.4, –7.4)</b>
<b>Race/ Ethnicity</b>				
White	1992–2007	<b>0.6 (0.1, 1.1)</b>	1992–2004	2.4 (–0.6, 5.4)
	2007–2011	<b>–4.5 (–8.2, –0.6)</b>	2004–2011	<b>–14.6 (–22.2, –6.1)</b>
Black	1992–2007	<b>1.8 (0.6, 3)</b>	1992–2008	0.9 (–2.2, 4)
	2007–2011	<b>–8.1 (–15.7, 0)</b>	2008–2011	–50.8 (–77.8, 9)
Hispanic	1992–2011	0.6 (–0.5, 1.7)	1992–2011	–2.9 (–6.2, 0.5)
API	1992–2011	<b>2.8 (0.8, 4.7)</b>	1992–2011	–2.9 (–8.2, 2.8)
<b>Age group (10 years)</b>				
00–09 years	1992–2011	0.5 (–2.4, 3.5)		
10–19 years	1992–2011	–0.6 (–1.7, 0.5)	1992–2011	–2.5 (–5.2, 0.3)
20–29 years	1992–2011	–0.4 (–1, 0.3)	1992–2008	–0.7 (–2.5, 1.2)
			2008–2011	<b>–40 (–60.7, –8.5)</b>
30–39 years	1992–2007	0.7 (–0.3, 1.6)	1992–2003	<b>6.7 (2.2, 11.4)</b>
	2007–2011	<b>–7.1 (–13.7, 0)</b>	2003–2011	<b>–17.7 (–25.3, –9.4)</b>
40–49 years	1992–2006	<b>2.4 (1, 3.7)</b>	1992–2000	8.9 (–1.6, 20.5)
	2006–2011	<b>–7 (–12.7, –0.8)</b>	2000–2011	<b>–11.5 (–18.6, –3.7)</b>



Nodular sclerosis				
	Not otherwise specified (9663 <sup>‡</sup> )		Cellular phase, Grades 1 and 2 (9664–9667 <sup>‡</sup> )	
	N= 11,135		N= 1,587	
	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
50–59 years	1992–2011	–1.7 (–3, –0.3)	1992–2011	–1.6 (–5.1, 1.9)
60–69 years	1992–2011	–0.9 (–2.5, 0.7)		
70–79 years	1992–2011	<b>2 (0.2, 3.8)</b>		
80+ years	1992–2011	1.3 (–0.6, 3.2)		
<b>Age groups</b>				
00–14 years	1992–2011	–0.8 (–2.5, 1)		
15–39 years	1992–2011	–0.3 (–0.8, 0.1)	1992–2008	–0.3 (–2.4, 1.9)
	1992–2005	<b>1.8 (0.5, 3.2)</b>	2008–2011	<b>–40.9 (–61.9, –8.2)</b>
40–54 years	2005–2011	<b>–5.5 (–9.4, –1.4)</b>	1992–1999	<b>11.1 (1.6, 21.4)</b>
			1999–2011	<b>–9.4 (–13.2, –5.4)</b>
55+ years	1992–2011	0.3 (–0.6, 1.2)	1992–2003	4 (–0.5, 8.7)
			2003–2011	<b>–15.9 (–21.8, –9.5)</b>
<b>Stage</b>				
Localized	1992–2011	<b>–3.5 (–4.5, –2.5)</b>		
Regional	1992–2011	0.4 (–0.1, 0.8)	1992–2004	2.3 (–0.1, 4.7)
			2004–2011	<b>–15.3 (–20.6, –9.5)</b>
Distant	1992–2011	<b>1.5 (0.3, 2.7)</b>		
NA and unstaged	1992–2011	–0.5 (–2.9, 1.9)		
<b>Tumor site</b>				
Nodal	1992–2009	0.1 (–0.3, 0.5)	1992–2004	2 (–1, 5.1)
	2009–2011	–8.4 (–18.3, 2.7)	2004–2011	<b>–15.1 (–21.5, –8.3)</b>
Extranodal	1992–2011	<b>2.3 (0.4, 4.2)</b>		
<b>Registry</b>				
Connecticut	1992–2003	<b>2.5 (0.7, 4.3)</b>	1992–2011	<b>–4.5 (–8.3, –0.5)</b>
	2003–2011	<b>–6.3 (–9.2, –3.3)</b>		
Detroit	1992–2011	–0.4 (–1.8, 1.1)	1992–2011	–0.8 (–4.7, 3.2)

Nodular sclerosis				
	Not otherwise specified (9663 <sup>‡</sup> )		Cellular phase, Grades 1 and 2 (9664–9667 <sup>‡</sup> )	
	N= 11,135		N= 1,587	
	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
Hawaii	1992–2011	1.8 (–0.7, 4.4)		
Iowa	1992–2011	–0.1 (–1.1, 0.8)	1992–2011	–2.9 (–6.2, 0.6)
New Mexico	1992–2011	<b>–3.1 (–5.1, –1)</b>		
Seattle	1992–2011	1 (–0.3, 2.3)		<b>–5.9 (–10.8, –0.7)</b>
Utah	1992–2011	<b>1.4 (0.1, 2.8)</b>		
Atlanta	1992–2011	–0.7 (–1.9, 0.6)		
San Francisco- Oakland	1992–2011	–0.9 (–2.3, 0.5)		
San Jose-Monterey	1992–2011	–0.4 (–1.9, 1.2)		
Los Angeles	1992–2011	0.2 (–0.7, 1.1)	1992–2004	<b>5.6 (1.2, 10.2)</b>
			2004–2011	<b>–16 (–26.6, –3.9)</b>
Alaska Natives				
Rural Georgia				

<sup>‡</sup> ICD-O-3 codes;

\* Joinpoint cannot process records when a dependent variable has a value of 0.

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**Table 3** Joinpoint average percent change (APC)\* and 95% confidence intervals (CI) for Hodgkin lymphoma incidence rates, by combined histologic subtypes and patient and tumor characteristics, 1992–2011, SEER (13 registries)

Combined Rates						
	Mixed cellularity + Not otherwise specified	Mixed cellularity + Lymphocyte depletion + Not otherwise specified	Mixed cellularity + Lymphocyte depletion + Not otherwise specified + Nodular sclerositis 9664–9667‡			
	N=6,739	N=7,042	N=8,629			
TOTAL	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
	1992 – 2011	0.9 (0.3, 1.5)	1992 – 1995 1995 – 2011	-6.7 (-15.4, 2.8) <b>1.4 (0.6, 2.1)</b>	1992–2011	0.1 (-0.4, 0.5)
<b>Sex</b>						
Male	1992 – 2011	0.5 (-0.1, 1.2)	1992 – 2011	0.3 (-0.4, 1)	1992–2011	-0.3 (-0.8, 0.3)
Female	1992 – 2000 2000 – 2011	-1 (-3.5, 1.6) <b>3.2 (1.8, 4.6)</b>	1992 – 2000 2000 – 2011	-1.5 (-4.1, 1.1) <b>3.3 (1.8, 4.8)</b>	1992–2011	0.5 (-0.1, 1.1)
<b>Race/Ethnicity</b>						
White	1992 – 2011	<b>0.8 (0.2, 1.4)</b>	1992 – 2011	0.7 (0, 1.3)	1992–2011	0 (-0.5, 0.4)
Black	1992 – 2000 2000 – 2011	-4.2 (-9, 0.9) <b>5.0 (2.0, 8.1)</b>	1992 – 2011	1.5 (-0.1, 3.0)	1992–2011	0.9 (-0.5, 2.2)
Hispanic	1992 – 2011	0.5 (-0.7, 1.7)	1992 – 2011	0.1 (-1.1, 1.4)	1992–2011	-0.3 (-1.3, 0.8)
API	1992 – 2011	<b>3.0 (1.1, 4.9)</b>	1992 – 2011	<b>2.1 (0.3, 4)</b>	1992–2011	1.0 (-0.7, 2.7)
AI/AN						
Unknown						

Combined Rates							
Mixed cellularity + Lymphocyte depletion + Not otherwise specified		Mixed cellularity + Lymphocyte depletion + Not otherwise specified		Mixed cellularity + Lymphocyte depletion + Not otherwise specified + Nodular sclerosis 9664-9667 <sup>‡</sup>		N=8,629	
Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
N=6,739		N=7,042		N=8,629			
Age group (10 years)							
00-09 years	1992-2011	2.3 (-0.8, 5.6)	1992-2011	2.3 (-0.8, 5.6)	1992-2011	1.2 (-1.7, 4.1)	
10-19 years	1992-2004	-2.3 (-4.7, 0.2)	1992-2003	-3.1 (-5.5, -0.6)	1992-2011	0.3 (-0.9, 1.5)	
	2004-2011	<b>9.2 (3.8, 14.9)</b>	2003-2011	<b>8.4 (4.5, 12.4)</b>			
20-29 years	1992-1996	<b>-14.2 (-24.9, -2)</b>	1992-1996	<b>-13.8 (-24.5, -1.7)</b>	1992-2011	0.4 (-0.8, 1.8)	
	1996-2011	<b>4.6 (2.8, 6.4)</b>	1996-2011	<b>4.6 (2.9, 6.4)</b>			
30-39 years	1992-2011	0.9 (-0.4, 2.1)	1992-2011	0.6 (-0.6, 1.8)	1992-2011	-0.1 (-1.0, 0.9)	
40-49 years	1992-2011	0.8 (-0.3, 1.9)	1992-2011	0.8 (-0.3, 1.9)	1992-2011	-0.1 (-1.1, 0.8)	
50-59 years	1992-2011	0.1 (-0.9, 1.2)	1992-2011	0 (-1.1, 1.1)	1992-2011	-0.1 (-1.1, 0.9)	
60-69 years	1992-2011	0 (-1.4, 1.4)	1992-2011	-0.4 (-1.7, 1.0)	1992-2011	-0.7 (-2.1, 0.7)	
70-79 years	1992-2011	0.3 (-1.0, 1.6)	1992-2011	-0.4 (-1.6, 0.9)	1992-2011	-0.8 (-1.8, 0.2)	
80+ years	1992-2011	<b>2.5 (1.0, 4.0)</b>	1992-2011	<b>2.5 (0.9, 4.2)</b>	1992-2011	<b>2.0 (0.4, 3.7)</b>	
Age groups							
00-14 years	1992-2011	<b>2.9 (0.9, 4.9)</b>	1992-2011	<b>2.9 (0.9, 4.9)</b>	1992-2011	1.8 (-0.1, 3.6)	
15-39 years	1992-1998	<b>-6.1 (-11, -0.9)</b>	1992-1998	<b>-6.0 (-10.4, -1.4)</b>	1992-2011	0.1 (-0.7, 0.8)	
	1998-2011	<b>3.8 (2.1, 5.5)</b>	1998-2011	<b>3.7 (2.2, 5.2)</b>			
40-54 years	1992-2011	0.5 (-0.4, 1.5)	1992-2011	0.5 (-0.4, 1.5)	1992-2011	-0.1 (-0.9, 0.7)	

Combined Rates									
N=6,739			N=7,042			N=8,629			
	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	
55+ years	1992 – 2011	0.6 (-0.1, 1.3)	1992 – 2011	0.3 (-0.5, 1.0)	1992–2011	-0.1 (-0.8, 0.6)			
<b>Stage</b>									
Localized	1992 – 2011	<b>-2.0 (-3.2, -0.9)</b>	1992 – 2011	<b>-2.2 (-3.3, -1.1)</b>	1992–2011	<b>-2.9 (-4, -1.9)</b>			
Regional	1992 – 2000	-1.2 (-3.5, 1.2)	1992 – 1994	-14.5 (-33.1, 9.2)	1992–2011	<b>1.1 (0.6, 1.7)</b>			
	2000 – 2011	<b>4.4 (2.9, 5.8)</b>	1994 – 2011	<b>3.0 (2.2, 3.7)</b>					
Distant	1992 – 2011	<b>1.4 (0.6, 2.3)</b>	1992 – 2011	<b>1.0 (0.1, 2)</b>	1992–2011	0.7 (-0.2, 1.6)			
NA and unstaged	1992 – 2011	-0.6 (-2.0, 0.9)	1992 – 2011	-0.5 (-1.7, 0.7)	1992–2011	-0.7 (-2.0, 0.6)			
<b>Tumor site</b>									
Nodal	1992 – 1997	-3.8 (-7.9, 0.6)	1992 – 1997	-4.1 (-8.1, 0.1)	1992–2011	0 (-0.5, 0.4)			
	1997 – 2011	<b>1.8 (0.9, 2.7)</b>	1997 – 2011	<b>1.6 (0.7, 2.6)</b>					
Extranodal					1992–2011	1.9 (0, 3.9)			
<b>Registry</b>									
Connecticut	1992 – 1995	<b>-20.5 (-35.8, -1.6)</b>	1992 – 1995	<b>-21.6 (-36.8, -2.6)</b>	1992–1995	<b>-16.1 (-29.1, -0.8)</b>			
	1995 – 2011	<b>2.8 (0.9, 4.7)</b>	1995 – 2011	<b>3.1 (1.3, 5.1)</b>	1995–2011	<b>1.5 (0, 3)</b>			
Detroit	1992 – 2011	0.2 (-1.2, 1.5)	1992 – 2011	0.1 (-1.3, 1.6)	1992–2011	-0.2 (-1.4, 1)			
Hawaii	1992 – 2011	0.6 (-1.7, 2.9)	1992 – 2011	0.2 (-2.1, 2.6)	1992–2011	0.3 (-1.9, 2.7)			
Iowa	1992 – 2011	1.8 (0, 3.6)	1992 – 2011	1.4 (-0.2, 3.1)	1992–2011	0.5 (-1.1, 2.1)			

Combined Rates									
Mixed cellularity + Lymphocyte depletion + Not otherwise specified			Mixed cellularity + Lymphocyte depletion + Not otherwise specified			Mixed cellularity + Lymphocyte depletion + Not otherwise specified + Nodular sclerosis 9664-9667 <sup>‡</sup>			
N=6,739			N=7,042			N=8,629			
Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
1992 – 1998	-10.2 (-22.3, 3.9)	1992 – 1999	-10.1 (-21.3, 2.7)	1992-1998	-10 (-18.9, -0.1)	1992-1998	-10 (-18.9, -0.1)		
1998 – 2005	<b>17.1 (3, 33.1)</b>	1999 – 2003	32.3 (-1.1, 96.6)	1998-2005	<b>12.7 (2.5, 24)</b>	1998-2005	<b>12.7 (2.5, 24)</b>		
2005 – 2011	-9.0 (-18.8, 2)	2003 – 2011	-5.5 (-12.1, 1.6)	2005-2011	-8.8 (-16.8, 0.1)	2005-2011	-8.8 (-16.8, 0.1)		
1992 – 2011	0.2 (-1.2, 1.5)	1992 – 2011	-0.1 (-1.3, 1.2)	1992-2011	<b>-1.3 (-2.4, -0.1)</b>	1992-2011	<b>-1.3 (-2.4, -0.1)</b>		
1992 – 2011	1.0 (-1.8, 3.9)	1992 – 2011	0.9 (-1.8, 3.7)	1992-2011	0.3 (-1.9, 2.5)	1992-2011	0.3 (-1.9, 2.5)		
1992 – 2011	1.1 (-0.9, 3.3)	1992 – 2011	0.7 (-1.3, 2.7)	1992-2011	0.3 (-1.5, 2.1)	1992-2011	0.3 (-1.5, 2.1)		
1992 – 2011	<b>3.0 (1.2, 4.8)</b>	1992 – 2011	<b>2.9 (1.1, 4.7)</b>	1992-2011	1.6 (-0.1, 3.2)	1992-2011	1.6 (-0.1, 3.2)		
1992 – 2011	0.9 (-0.7, 2.6)	1992 – 2011	0.9 (-0.8, 2.5)	1992-2011	0.4 (-1, 1.9)	1992-2011	0.4 (-1, 1.9)		
1992 – 2011	0.1 (-1.0, 1.3)	1992 – 2011	-0.3 (-1.4, 0.8)	1992-2011	-0.5 (-1.5, 0.6)	1992-2011	-0.5 (-1.5, 0.6)		
Alaska Natives									
Rural Georgia									

<sup>‡</sup> ICD-O-3 codes;

\* Joinpoint cannot process records when a dependent variable has a value of 0.