

Changing Incidence of Hodgkin Lymphoma Histologic Subtypes: Risk Factor Trends or Evolving Diagnostic Practice?

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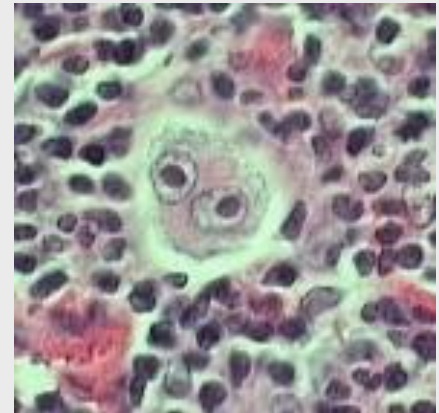


Background



Hodgkin lymphoma (HL)

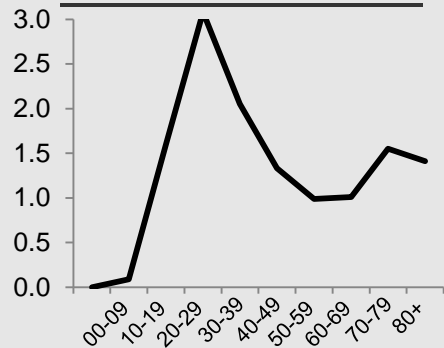
- Relatively rare B-cell malignancy
- Marked by HETEROGENEITY!
 - Epidemiology, pathology, outcomes
- Pathology
 - Complex, variable appearance
- WHO classification since 2001
 - Classical HL (cHL)
 - Nodular sclerosis (NS)
 - Mixed cellularity (MC)
 - Lymphocyte depletion (LD)
 - Lymphocyte rich (LR)
 - Nodular lymphocyte predominance (nLP)



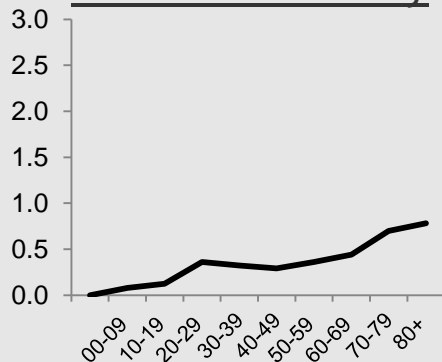
Hodgkin lymphoma (HL)

- Epidemiologic variation
 - CLASSICAL HL

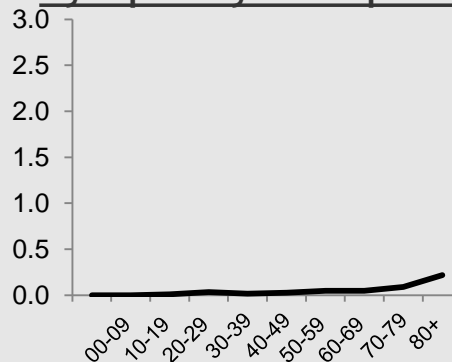
Nodular sclerosis



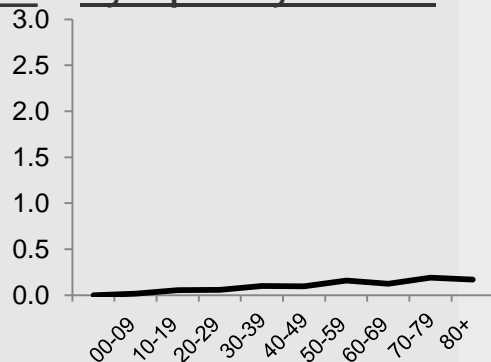
Mixed cellularity



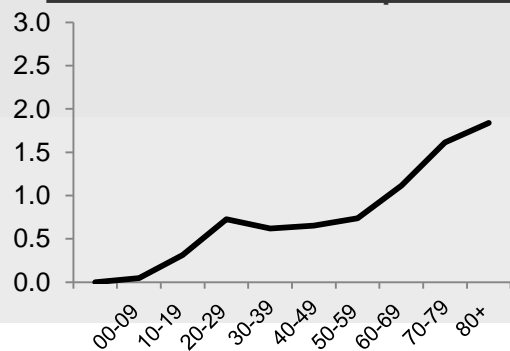
Lymphocyte depletion



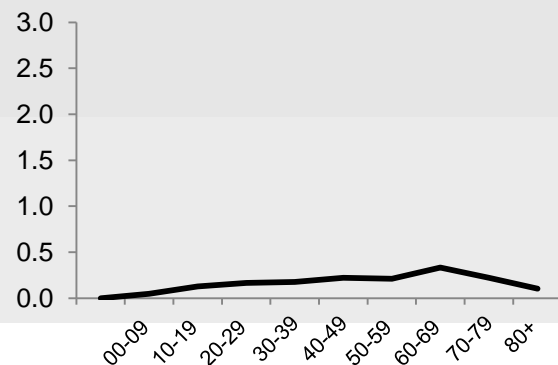
Lymphocyte rich



Not otherwise specified*



- NODULAR LYMPHOCYTE PREDOMINANCE



*NOS=ICD-O-3 category (9650) for cHL without further histologic subtyping



Hodgkin lymphoma (HL) trends

- Declining rates for MC
 - 6% per year 1992 to 2001 (SEER data)
- Increasing rates of NOS
 - 4% per year 1992 to 2001 (SEER data)
- Trends striking
 - Directions opposing
 - Persistent over time, seen in other studies
- Understanding MC and NOS trends important
 - Evaluate in greater detail, given HL heterogeneity
 - e.g., age, sex, race/ethnicity, etc.



Study approaches

- Evaluate detailed HL incidence rate trends by histologic subtype
 - Update trends using newest data
 - Large case series for rare subtypes, detailed analyses
- Test hypothesis that \downarrow MC rates \rightarrow \uparrow NOS rates
 - Misclassification of MC: “Case transfer” over time
- Gain insight into possible diagnostic and classification issues relevant to NOS rate \uparrow
 - Review of NOS pathology reports



Methods: 1-Rate trends

- Incidence data
 - SEER13 database
 - All new incident cases
 - Primary cHL (ICD-O-3 codes 9650-9667)
 - NS: 9663-9667
 - MC: 9652
 - LR: 9651
 - LD: 9653
 - NOS: 9650
 - nLP (9659)
 - Diagnosis years 1992 through 2011
 - N=21,372 HL cases



Methods: 1-Rate trends

- Age-adjusted rates, 95% confidence intervals (CI)
 - Histologic type
 - 10-year age groups
 - Age groups 0-14, 15-39, 40-54 and 55
 - Gender
 - Race/ethnicity
 - Stage (localized, regional, distant, unknown)
 - Tumor site (nodal, extranodal)
 - Year of diagnosis
 - SEER registry
- SEER*Stat



Methods: 1-Rate trends

- Joinpoint (segmented linear) regression analysis
 - Identifies significant changes in annual rates over time (trend segment)
 - Calculates **annual percent change (APC)** and 95% CI in annual rates within each trend segment
- 5-year incidence rates
 - 1992-96, 1997-2001, 2002-2006, 2007-2011
 - Compared using incidence rate ratios (IRRs) and 95% confidence intervals (CI)



Methods: 2- MC → NOS

- Compare MC and NOS rates in earliest and latest 5-year periods (1992-96 vs 2007-11)
 - IRRs
 - If initial big differences in subtype patterns ↓ = case transfer
- Combined MC+NOS rates
 - Combining increasing rates with decreasing rates
 - No rate trends = case transfer
 - Joinpoint regression



Methods: 3-Dx/classification issues

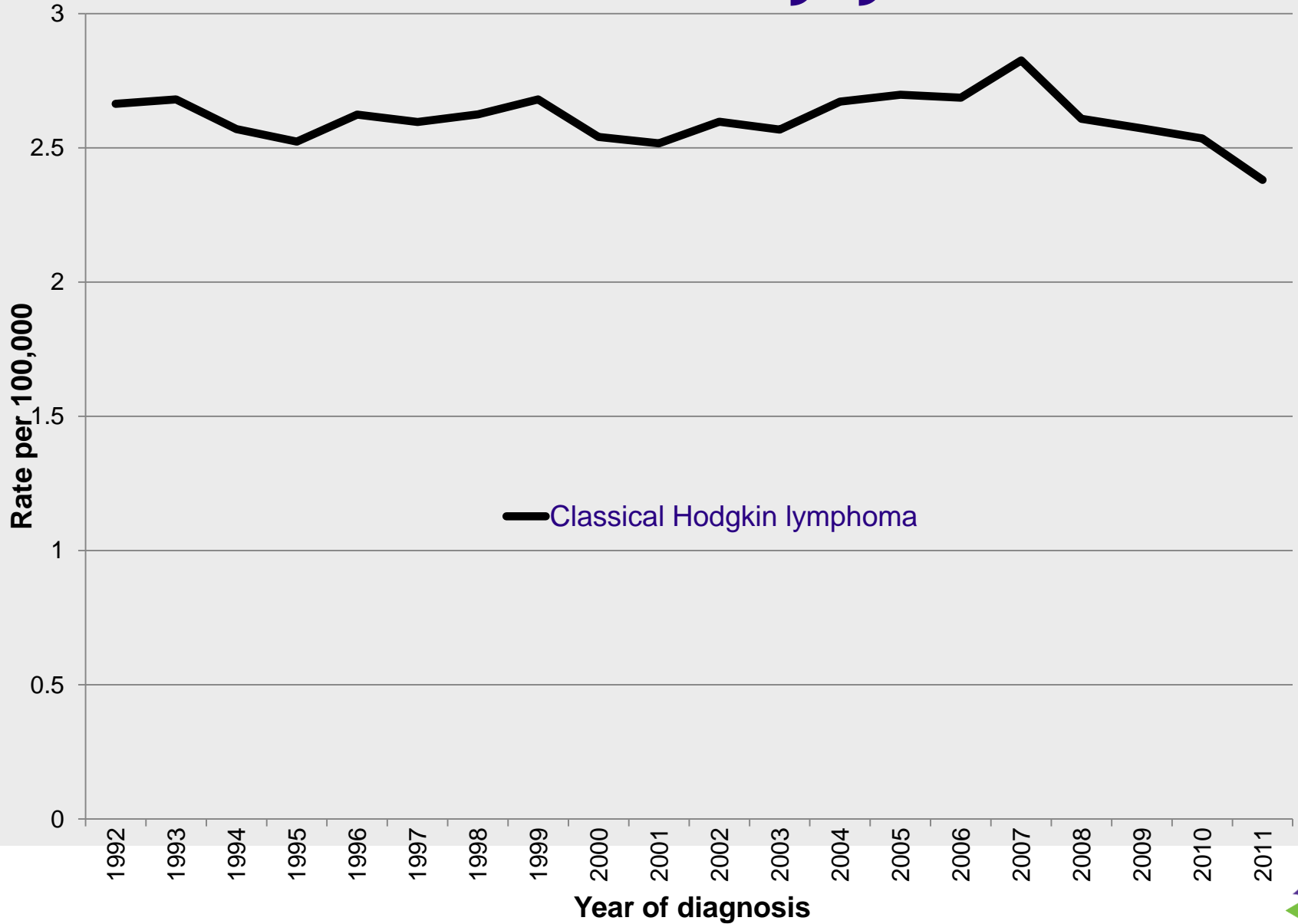
- QC at Greater Bay Area Cancer Registry
- All 286 incident HL NOS cases reported to SEER
 - Dx years 2007-11
 - Epath reports available for an efficient review
- QC specialist reviewed epath text and Eureka DMS data
- Documented set of factors
 - Related to use of the NOS classification
 - e.g., NOS justified? Specimen adequacy mentioned?
 - Other tumor/clinical characteristics from SEER
 - e.g., biopsy type? Facility type?



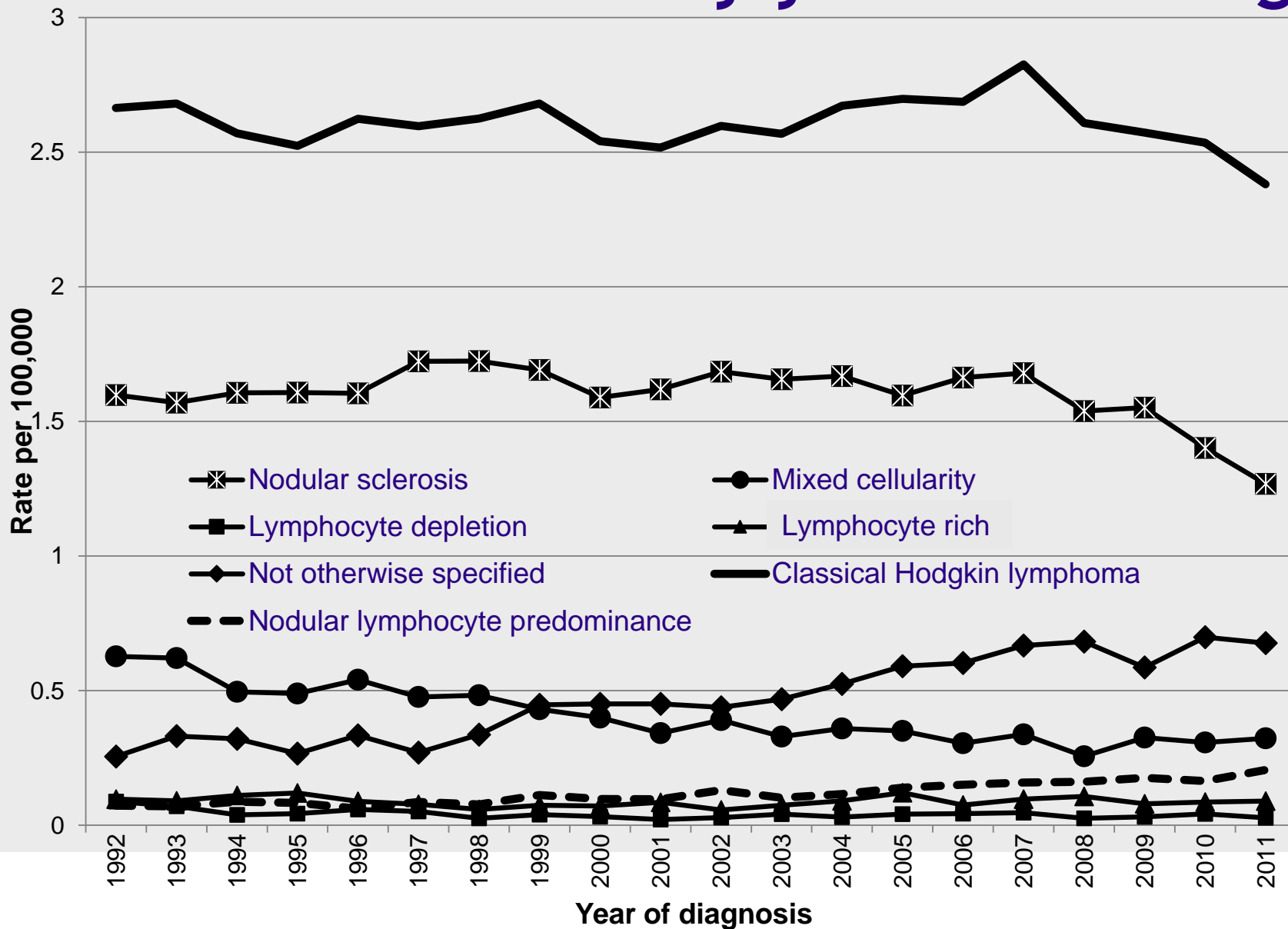
Results: 1-Trends



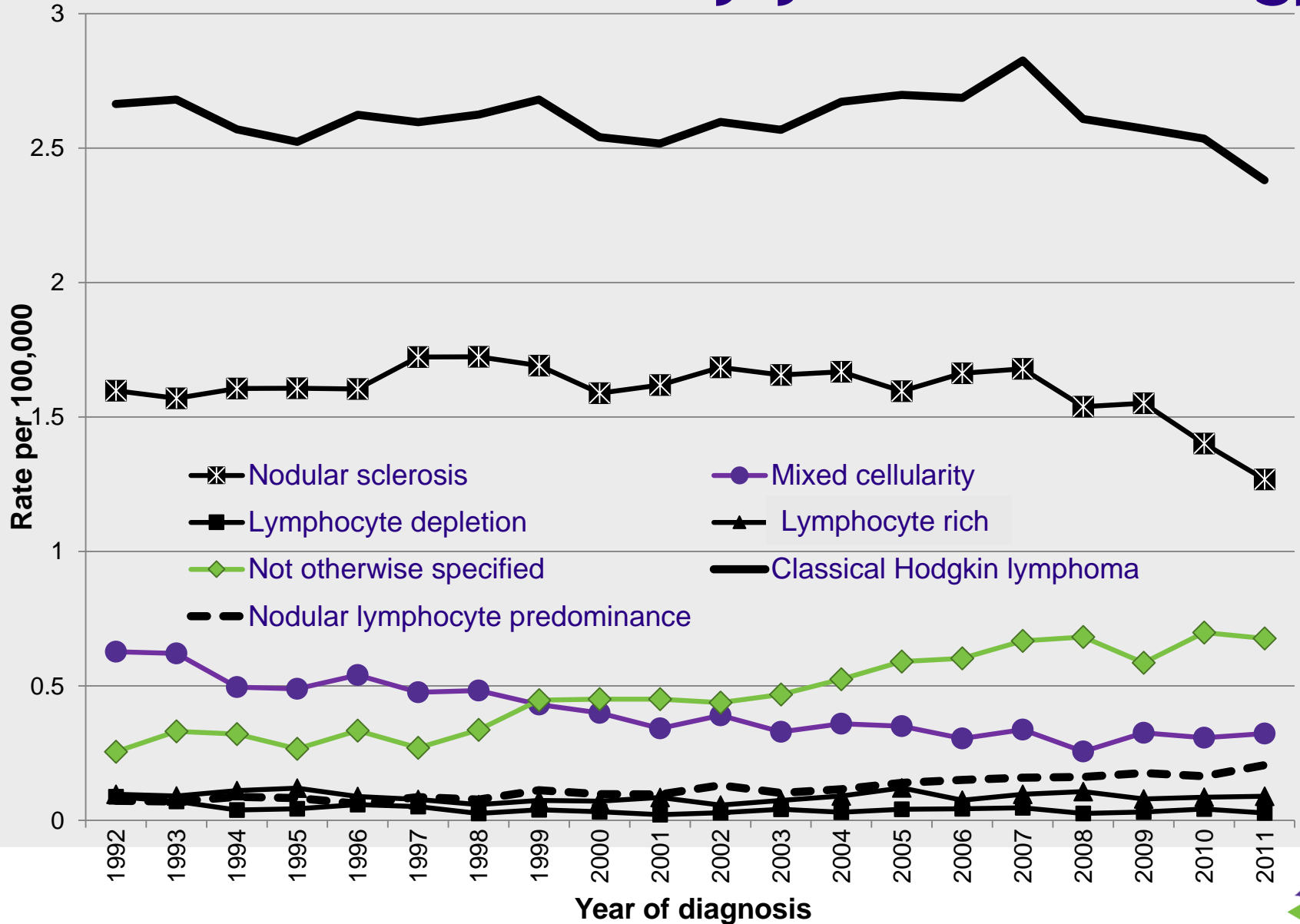
Results: cHL rates by year



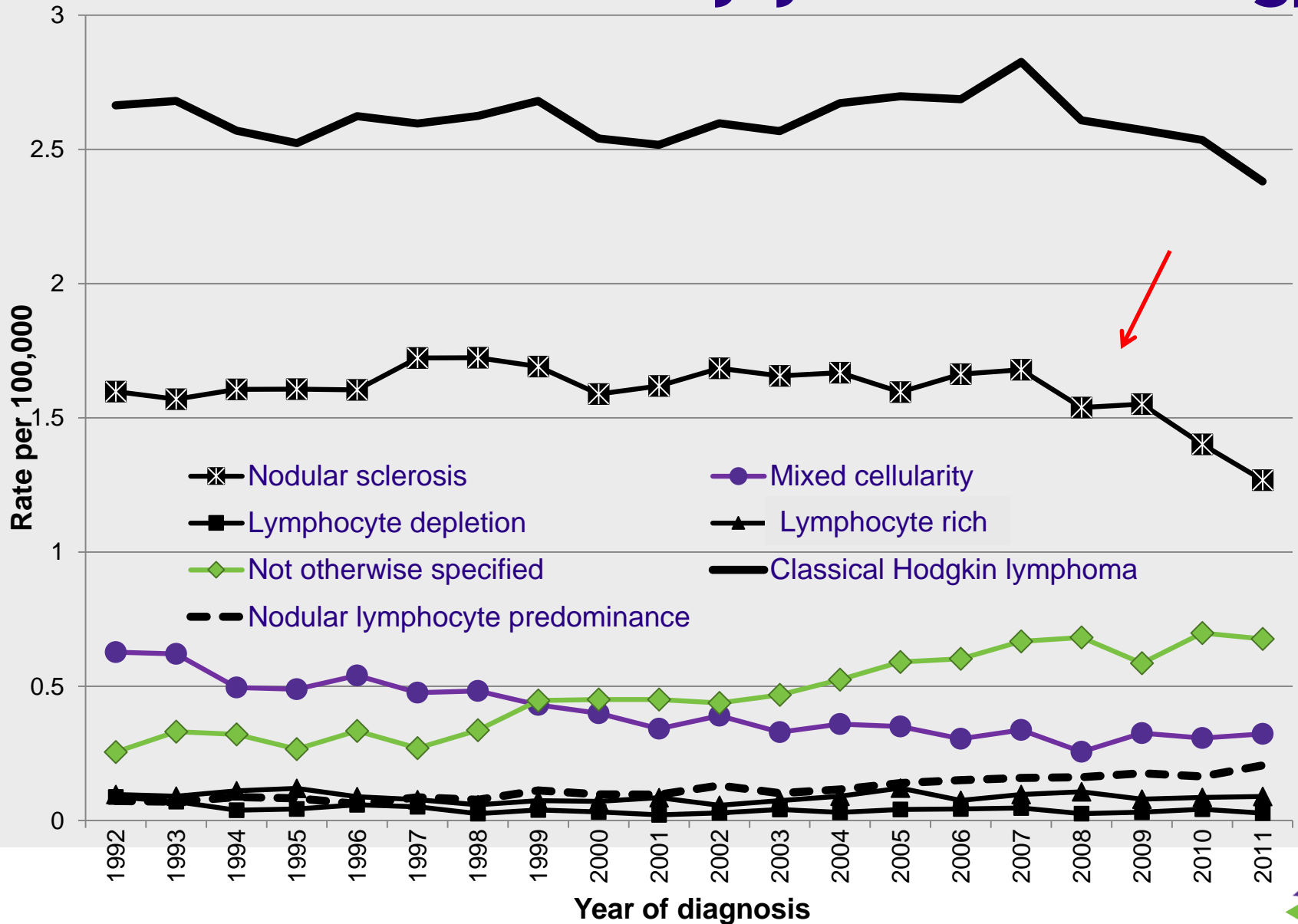
Results: cHL rates by year & histology



Results: cHL rates by year & histology

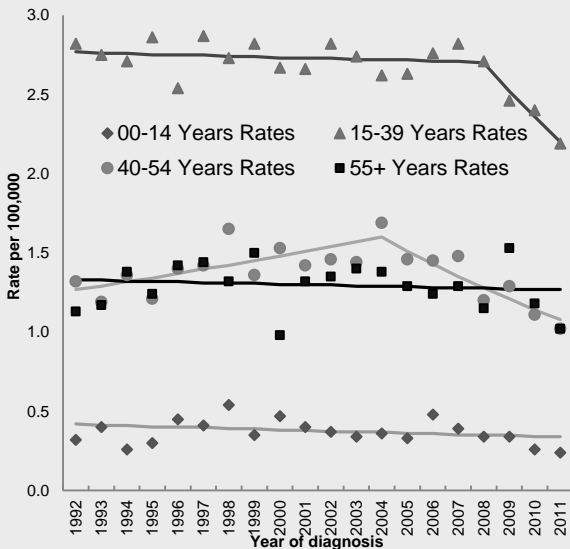


Results: cHL rates by year & histology

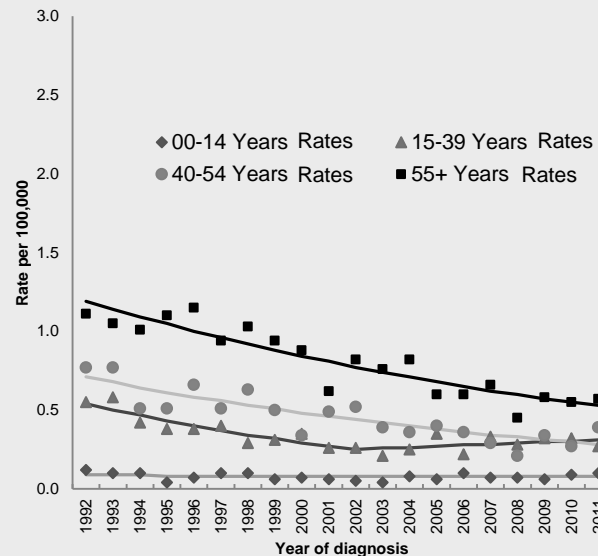


Results: Rates, Joinpoint trends by age

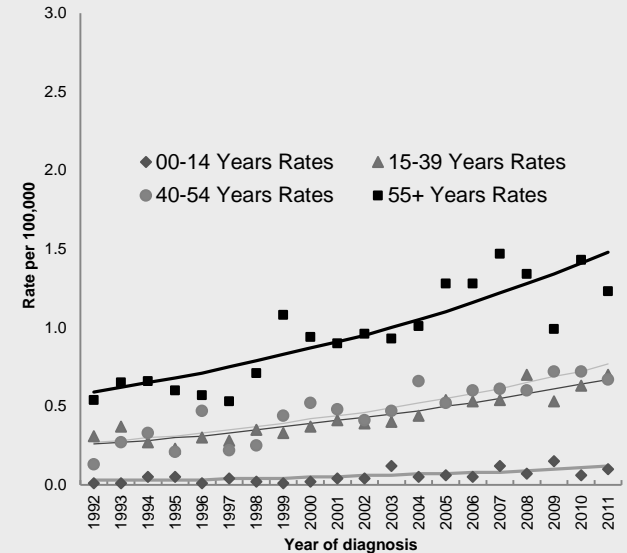
Nodular sclerosis



Mixed cellularity



Not otherwise specified

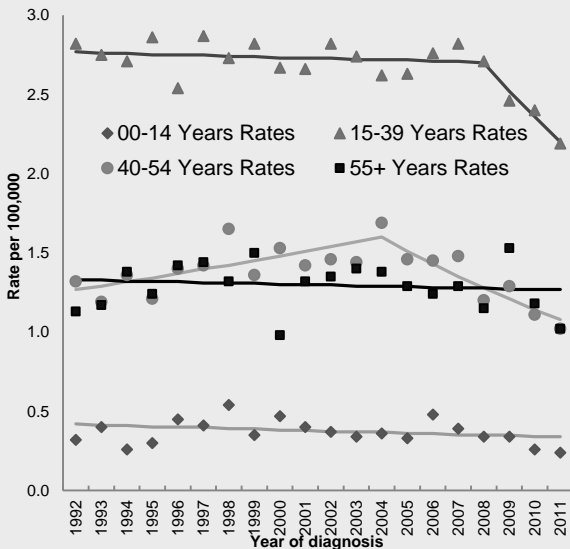


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40-54	1992 - 2004	1.9 (0.6, 3.3)	1992 - 2011	-4.7 (-6.1, -3.3)	1992 - 2011	5.7 (3.9, 7.6)
	2004 - 2011	-5.4 (-8.3, -2.6)				
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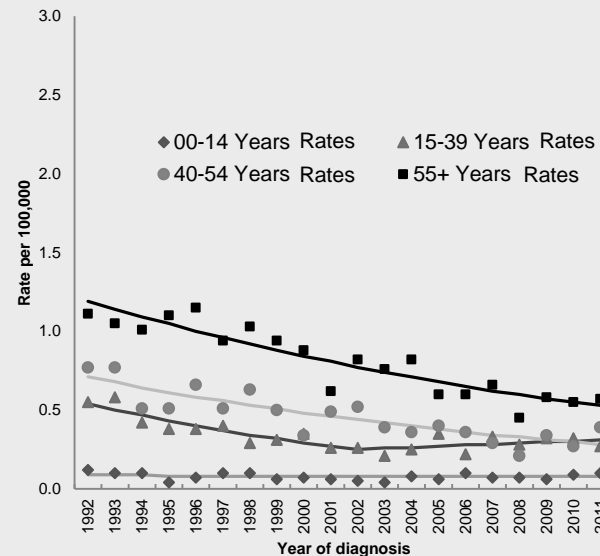


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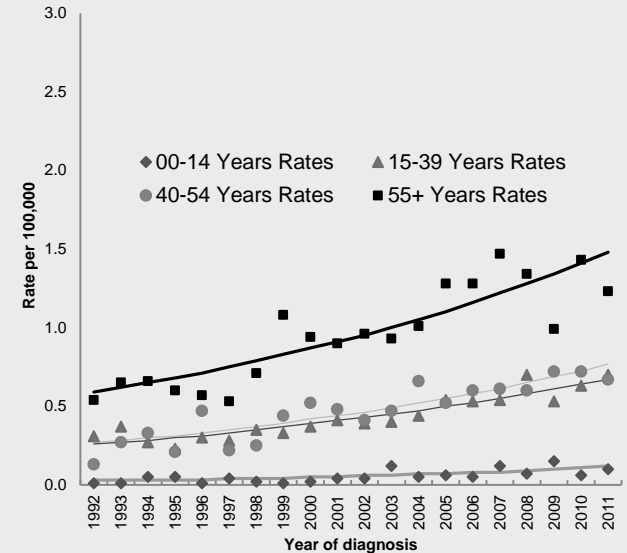
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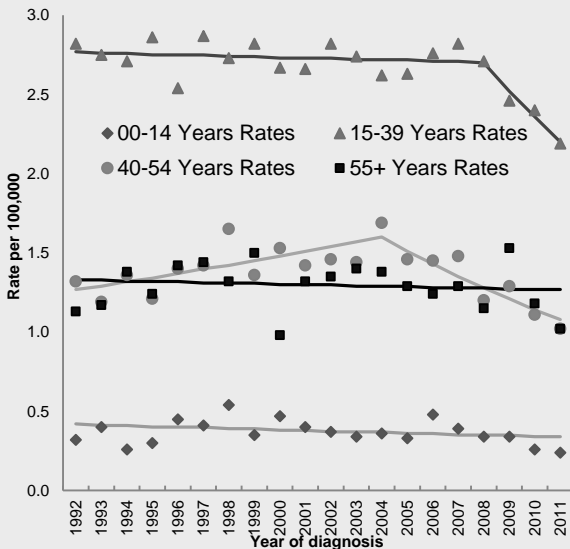


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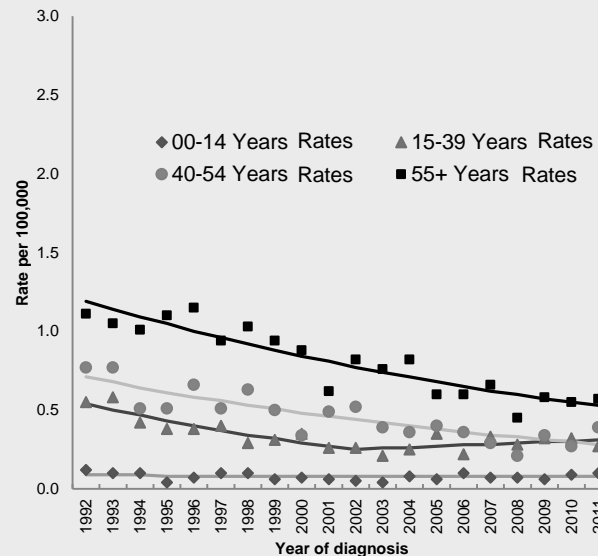


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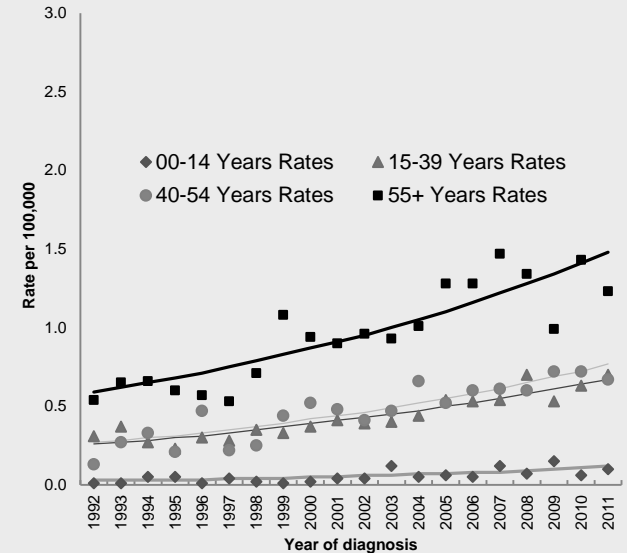
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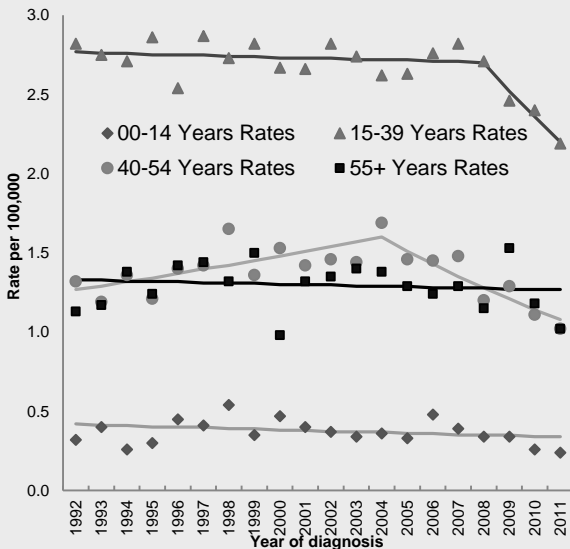


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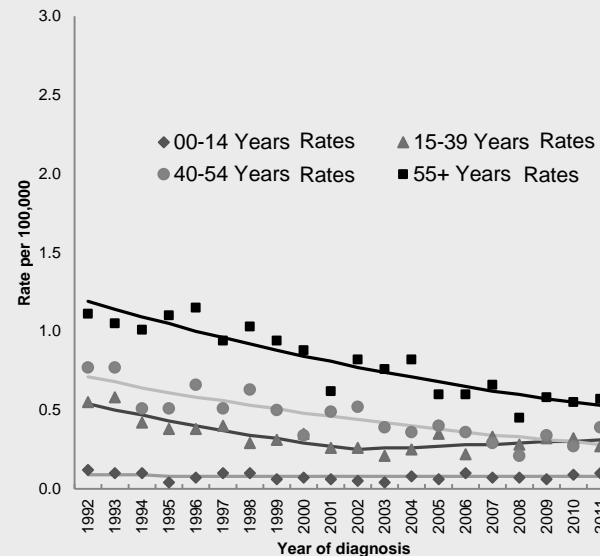


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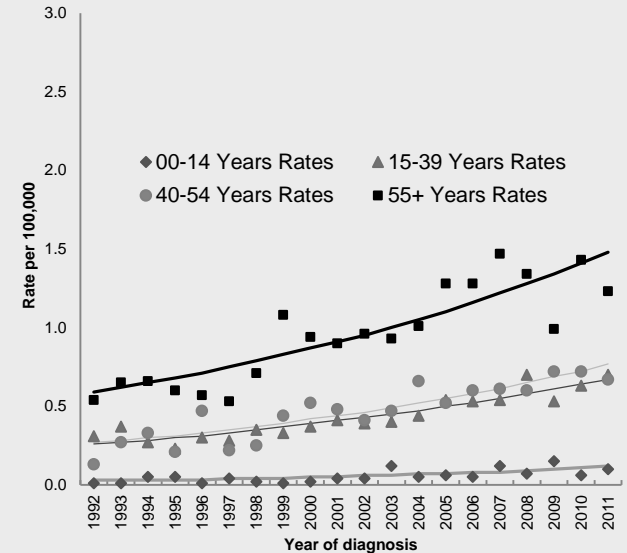
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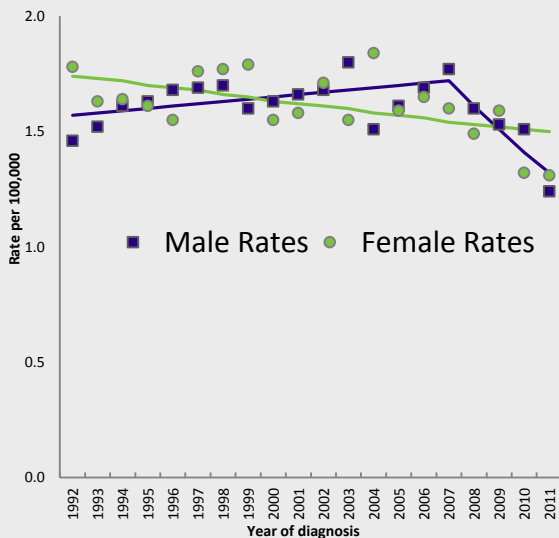


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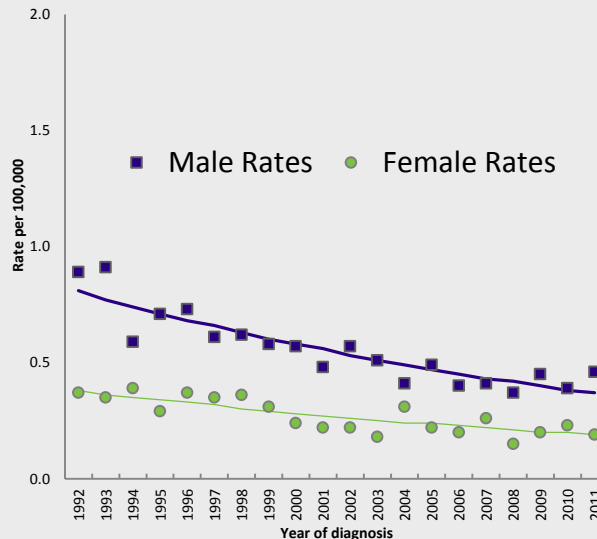


Results: Rates, Joinpoint trends by sex

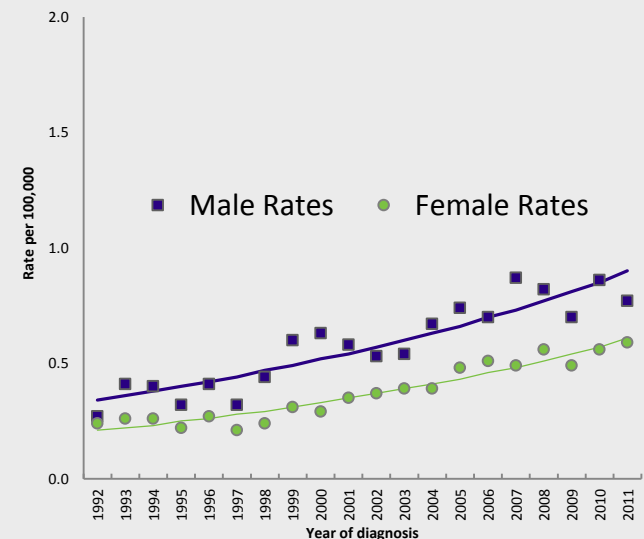
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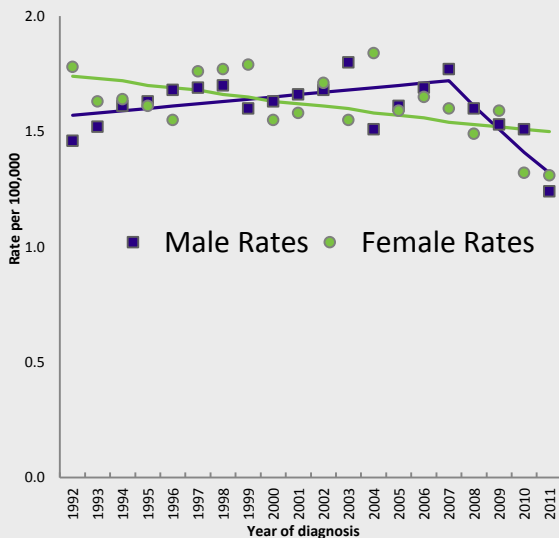


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Male	1992 - 2007	0.6 (0, 1.3)	1992 - 2011	-4.1 (-5, -3.2)	1992 - 2011	5.2 (3.9, 6.5)
	2007 - 2011	-6.4 (-11, -1.5)				
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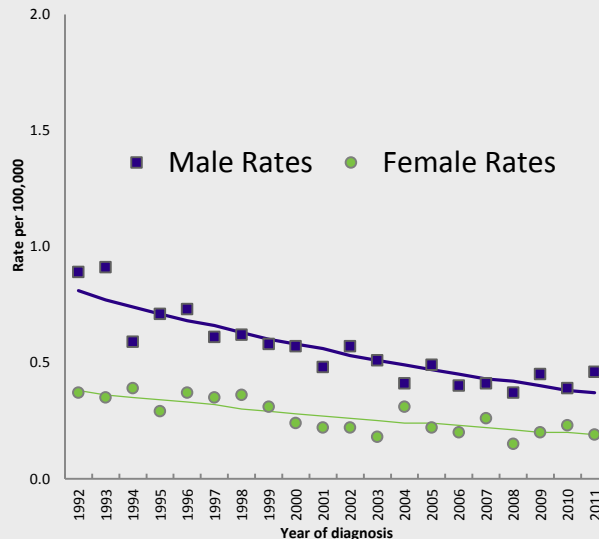


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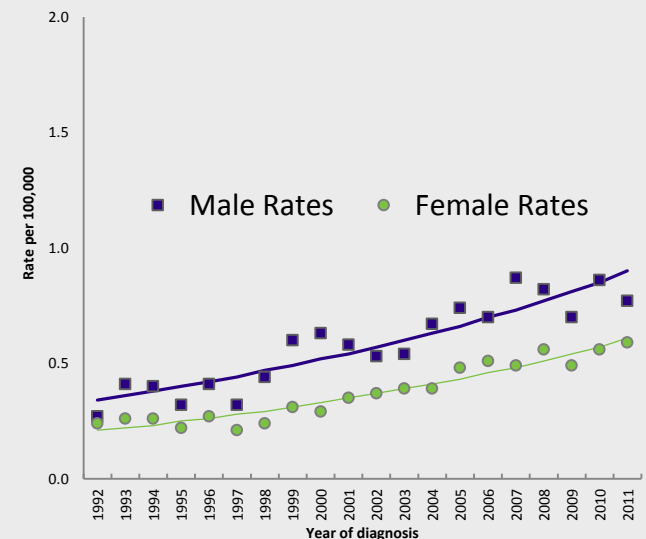
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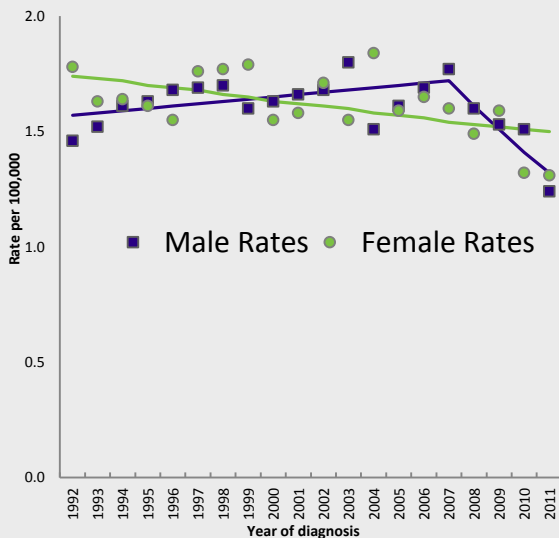


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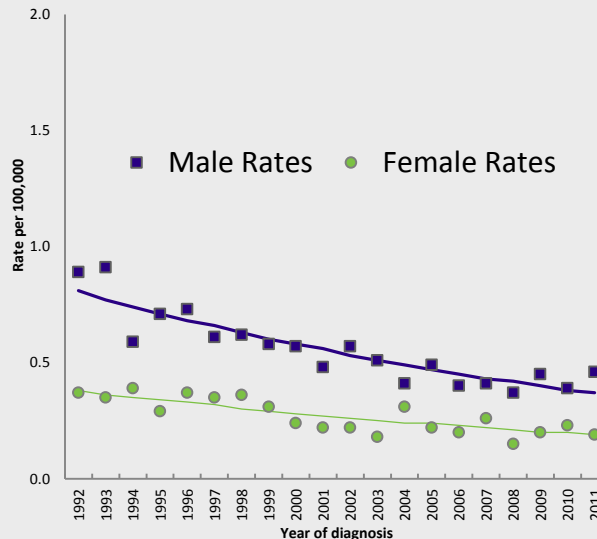


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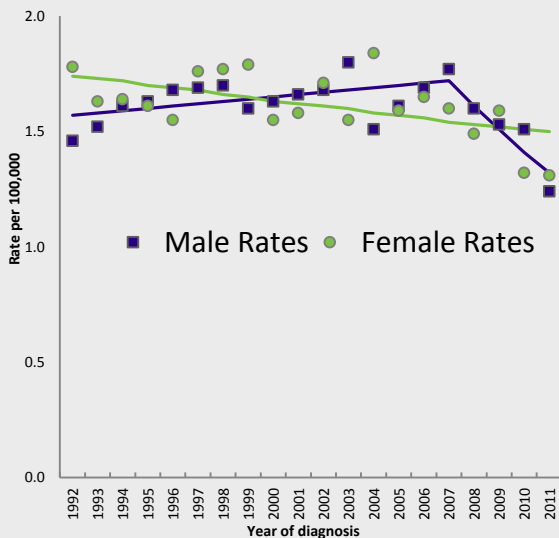


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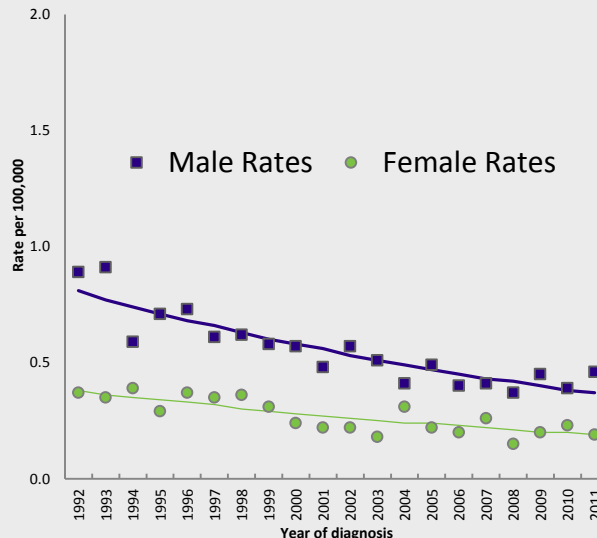


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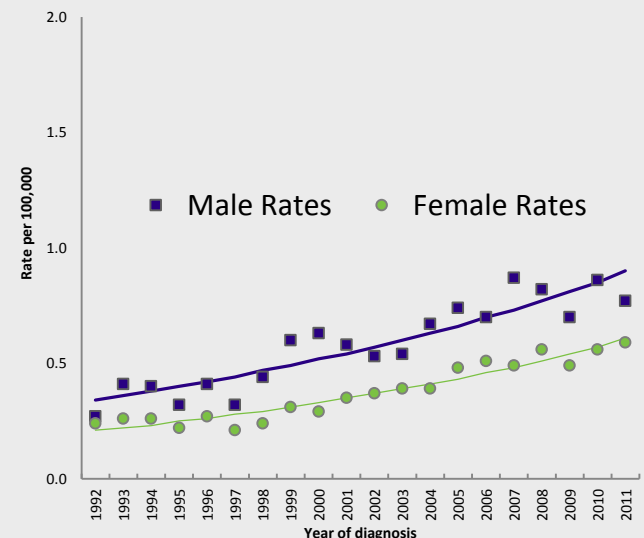
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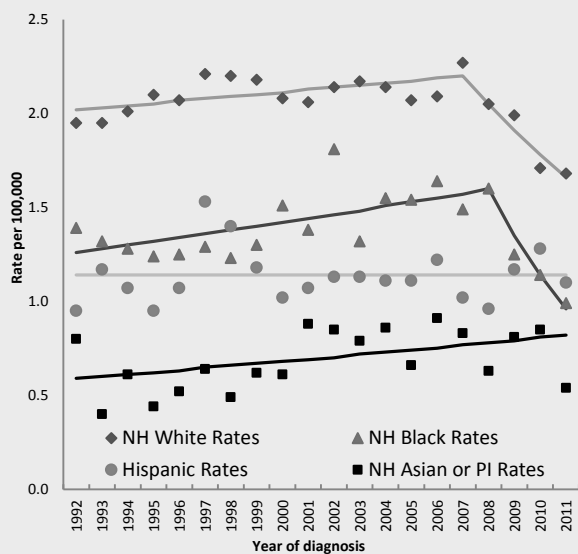


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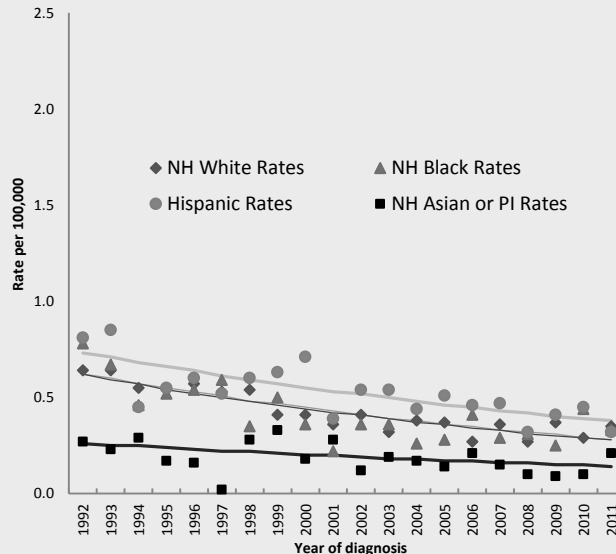


Results: Rates, Joinpoint trends by race

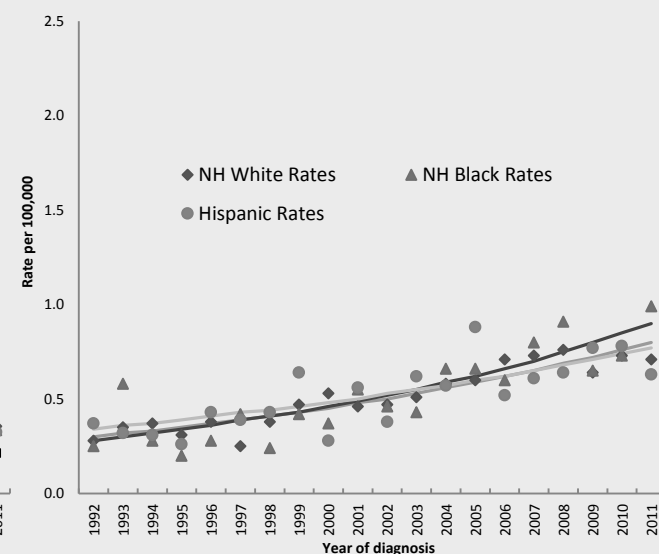
Nodular sclerosis



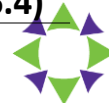
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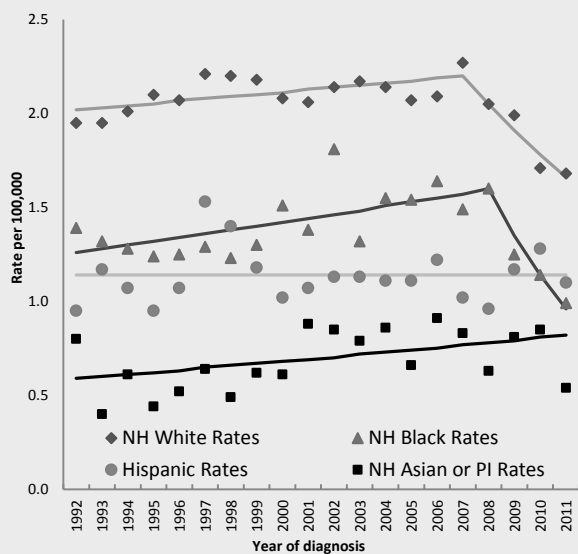


RACE	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
White	1992 - 2007	0.6 (0.1, 1)	1992 - 2011	-4.1 (-5, -3.2)	1992 - 2011	5.3 (4.2, 6.4)
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Black	1992 - 2008	1.5 (0.5, 2.6)	1992 - 2011	-4.1 (-5.9, -2.4)	1992 - 2011	6.2 (4.2, 8.3)
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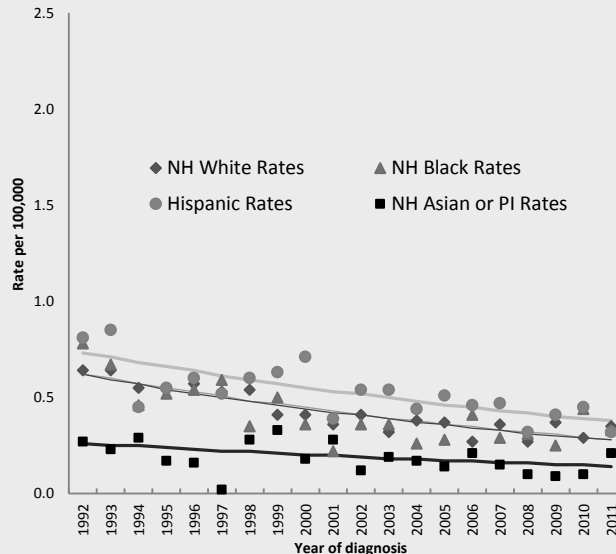


Results: Rates, Joinpoint trends by race

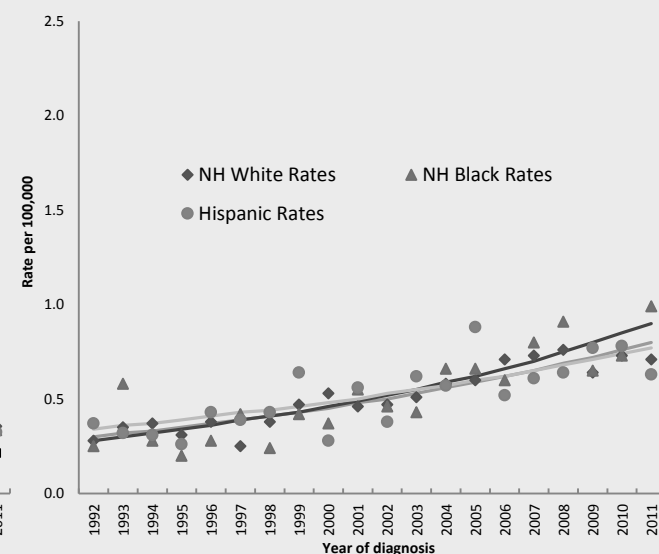
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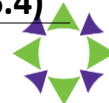
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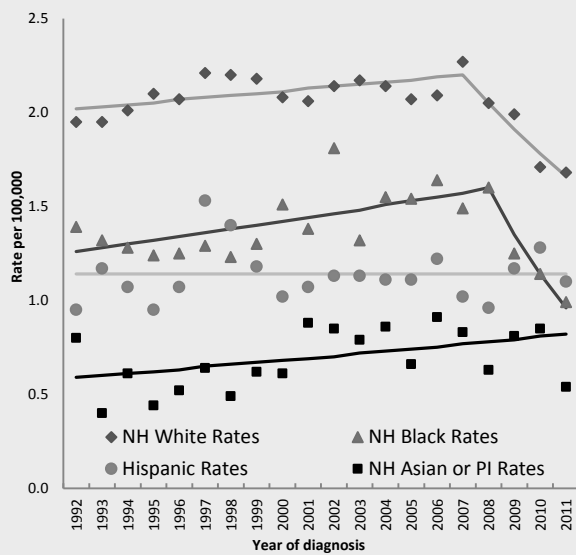


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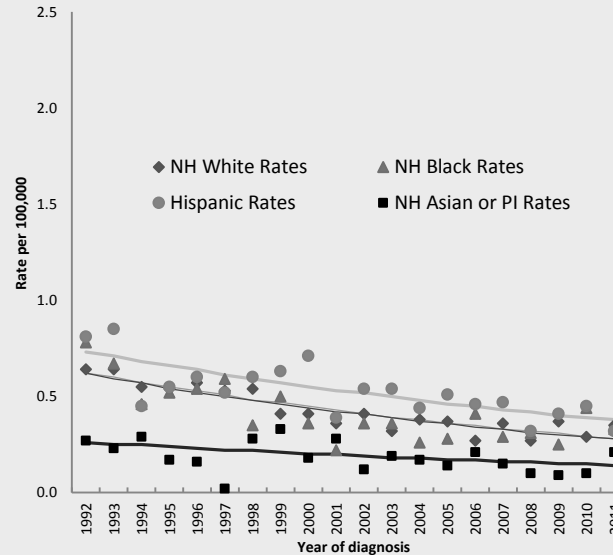


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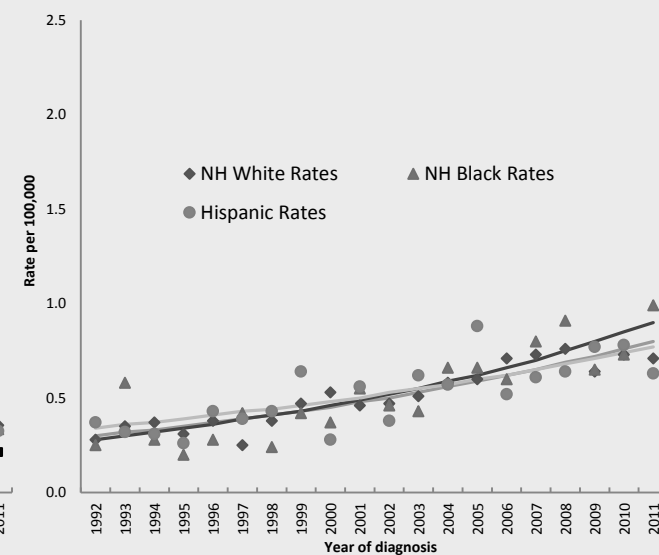
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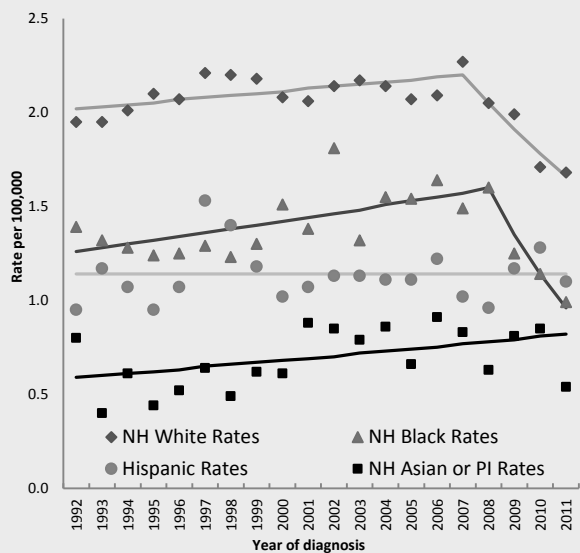


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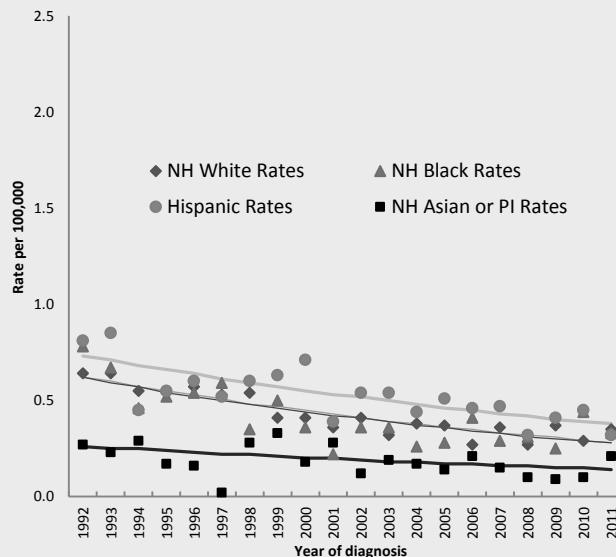


Results: Rates, Joinpoint trends by race

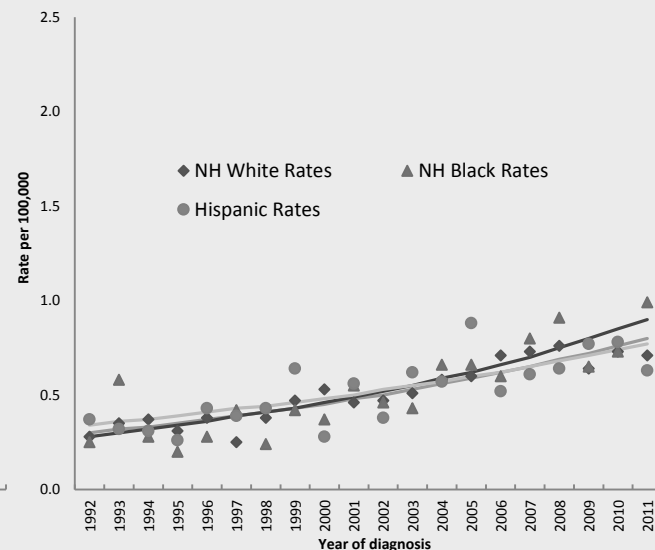
Nodular sclerosis



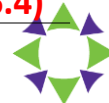
Mixed cellularity



Not otherwise specified



RACE	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
White	1992 - 2007	0.6 (0.1, 1)	1992 - 2011	-4.1 (-5, -3.2)	1992 - 2011	5.3 (4.2, 6.4)
	2007 - 2011	-6.7 (-10.2, -3.2)				
Black	1992 - 2008	1.5 (0.5, 2.6)	1992 - 2011	-4.1 (-5.9, -2.4)	1992 - 2011	6.2 (4.2, 8.3)
	2008 - 2011	-15.6 (-27.2, -2.2)				
Hispanic	1992 - 2011	0 (-1, 1)	1992 - 2011	-3.4 (-4.8, -2.1)	1992 - 2011	4.4 (2.4, 6.4)
API/AN	1992 - 2011	1.7 (-0.1, 3.6)	1992 - 2011	-3.1 (-6.1, -0.1)		



Summary: Rates, trends

- MC rates ↓, NOS rates ↑
 - Uniform across gender, age group, race/ethnicity, tumor stage, tumor site, SEER registry
 - *Suggestive of artifactual changes*
- NS rates stable over the first 15 years, then ↓
 - Variation by gender and age
 - *Suggestive of a true incidence change*



Results: 2- MC → NOS



Results: MC and NOS

- In 1992-96
 - NOS rates ~ **half** MC rates (IRR 0.55 (0.49, 0.61))
 - Same for most patient and tumor characteristics
- In 2007-11
 - NOS rates ~ **2X** MC rates (IRR 2.14 (1.94, 2.35))
 - Same for most patient and tumor characteristics
- 2007-11 NOS rates \approx 1992-96 MC rates overall
 - IRR 1.19 (1.1, 1.3)
- However, 2007-11 NOS rates $>$ 1992-96 MC rates
 - Selected patient categories



Results: MC + NOS combined rates

	MC + NOS	
	N=6,739	
	Interval (yrs)	APC (95% CI)
TOTAL		
	1992 - 2011	0.9 (0.3, 1.5)
Sex		
Male	1992 - 2011	0.5 (-0.1, 1.2)
Female	1992 - 2000	-1 (-3.5, 1.6)
	2000 - 2011	3.2 (1.8, 4.6)
Race/Ethnicity		
White	1992 - 2011	0.8 (0.2, 1.4)
Black	1992 - 2000	-4.2 (-9, 0.9)
	2000 - 2011	5.0 (2.0, 8.1)
Hispanic	1992 - 2011	0.5 (-0.7, 1.7)
API	1992 - 2011	3.0 (1.1, 4.9)

- Minimal (<1%) APC overall

	MC + NOS	
	N=6,739	
	Interval (yrs)	APC (95% CI)
Age groups		
00-14 years	1992 - 2011	2.9 (0.9, 4.9)
15-39 years	1992 - 1998	-6.1 (-11, -0.9)
	1998 - 2011	3.8 (2.1, 5.5)
40-54 years	1992 - 2011	0.5 (-0.4, 1.5)
55+ years	1992 - 2011	0.6 (-0.1, 1.3)
Stage		
Localized	1992 - 2011	-2.0 (-3.2, -0.9)
Regional	1992 - 2000	-1.2 (-3.5, 1.2)
	2000 - 2011	4.4 (2.9, 5.8)
Distant	1992 - 2011	1.4 (0.6, 2.3)
NA, unstaged	1992 - 2011	-0.6 (-2.0, 0.9)
Tumor site		
Nodal	1992 - 1997	-3.8 (-7.9, 0.6)
	1997 - 2011	1.8 (0.9, 2.7)
Extranodal		



Results: MC + NOS combined rates

	MC + NOS	
	N=6,739	
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TOTAL		
	1992 - 2011	0.9 (0.3, 1.5)
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Male	1992 - 2011	0.5 (-0.1, 1.2)
Female	1992 - 2000	-1 (-3.5, 1.6)
	2000 - 2011	3.2 (1.8, 4.6)
Race/Ethnicity		
White	1992 - 2011	0.8 (0.2, 1.4)
Black	1992 - 2000	-4.2 (-9, 0.9)
	2000 - 2011	5.0 (2.0, 8.1)
Hispanic	1992 - 2011	0.5 (-0.7, 1.7)
API	1992 - 2011	3.0 (1.1, 4.9)

	MC + NOS	
	N=6,739	
	Interval (yrs)	APC (95% CI)
Age groups		
00-14 years	1992 - 2011	2.9 (0.9, 4.9)
15-39 years	1992 - 1998	-6.1 (-11, -0.9)
	1998 - 2011	3.8 (2.1, 5.5)
40-54 years	1992 - 2011	0.5 (-0.4, 1.5)
55+ years	1992 - 2011	0.6 (-0.1, 1.3)
Stage		
Localized	1992 - 2011	-2.0 (-3.2, -0.9)
Regional	1992 - 2000	-1.2 (-3.5, 1.2)
	2000 - 2011	4.4 (2.9, 5.8)
Distant	1992 - 2011	1.4 (0.6, 2.3)
NA, unstaged	1992 - 2011	-0.6 (-2.0, 0.9)
Tumor site		
Nodal	1992 - 1997	-3.8 (-7.9, 0.6)
	1997 - 2011	1.8 (0.9, 2.7)
Extranodal		

- Significant increases still found
 - Females and blacks after 2000
 - Whites and APIs
 - Young adults starting in 1998 after a prior decline



Results: Other subtypes

- LD (rare subtype, considered a stage of MC)



Results: Other subtypes

- LD (rare subtype, considered a stage of MC)

	Lymphocyte depletion	
	N=303	
	Interval (yrs)	APC (95% CI)
TOTAL		
	1992 - 2011	-3.6 (-5.6, -1.5)
Sex		
Male	1992 - 2011	-5.7 (-8.3, -3)
Female		
Race/Ethnicity		
White	1992 - 2011	-3.5 (-6, -0.9)
Black		
Hispanic		
Age groups		
00-14 years		
15-39 years	1992 - 2011	-0.7 (-3, 1.7)
40-54 years		
55+ years	1992 - 2011	-5.8 (-8.6, -2.8)



Results: Other subtypes

- NS (two subtype groups)
 - NS NOS (9663)
 - 87% of all NS cases
 - NS cellular phase, grades 1 and 2 (9664-9667)



Results: Other subtypes

- NS (two subtype groups)
 - NS NOS (9663)
 - 87% of all NS cases
 - NS cellular phase, grades 1 and 2 (9664-9667)

9663

9664-9667

AGE	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
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)
			2008-2011	-40.9 (-61.9, -8.2)
40-54 years	1992-2005	1.8 (0.5, 3.2)	1992-1999	11.1 (1.6, 21.4)
	2005-2011	-5.5 (-9.4, -1.4)	1999-2011	-9.4 (-13.2, -5.4)
55+ years	1992-2011	0.3 (-0.6, 1.2)	1992-2003	4 (-0.5, 8.7)

SEX	Interval (yrs)	APC (95% CI)	Interval (yrs)	APC (95% CI)
Male	1992-2011	0.2 (-0.4, 0.7)	1992-1994	38 (-6.6, 103.9)
			1994-2008	-2.4 (-4.2, -0.7)
			2008-2011	-34.1 (-49.9, -13.3)
Female	1992-2011	-0.6 (-1.2, 0.1)	1992-2003	3.6 (0.4, 6.9)
			2003-2011	-13.6 (-19.4, -7.4)



Results: Combined MC+NOS+LD+NS 9664-67

	MC + NOS + LD + NS 9664=9667	
	N=8,629	
	Interval (yrs)	APC (95% CI)
TOTAL		
	1992 - 2011	0.1 (-0.4, 0.5)
Sex		
Male	1992 - 2011	-0.3 (-0.8, 0.3)
Female	1992 - 2000 2000 - 2011	0.5 (-0.1, 1.1)
Race/Ethnicity		
White	1992 - 2011	0 (-0.5, 0.4)
Black	1992 - 2000 2000 - 2011	0.9 (-0.5, 2.2)
Hispanic	1992 - 2011	-0.3 (-1.3, 0.8)
API	1992 - 2011	1.0 (-0.7, 2.7)

	MC + NOS + LD + NS 9664=9667	
	N=8,629	
	Interval (yrs)	APC (95% CI)
Age groups		
00-14 years	1992-2011	1.8 (-0.1, 3.6)
15-39 years	1992-2011	0.1 (-0.7, 0.8)
40-54 years	1992-2011	-0.1 (-0.9, 0.7)
55+ years	1992-2011	-0.1 (-0.8, 0.6)
Stage		
Localized	1992-2011	-2.9 (-4, -1.9)
Regional	1992-2011	1.1 (0.6, 1.7)
Distant	1992-2011	0.7 (-0.2, 1.6)
NA, unstaged	1992-2011	-0.7 (-2.0, 0.6)
Tumor site		
Nodal	1992-2011	0 (-0.5, 0.4)
Extranodal	1992-2011	1.9 (0, 3.9)

- For combined MC/NOS/LD/NS 9664-9667 rates
 - **No time trends** except for
 - Persons over age 80 (APC= 2.0 (0.4, 3.7))
 - Localized and regional disease



Summary: 2- MC and NOS

- Misclassification of true MC as NOS over time suggested by:
 - Opposing directions of MC and NOS trends
 - Minimal trends in combined MC/NOS rates overall
- Broader misclassification suggested by
 - Uniform declines in LD and NS codes 9664-9667
 - **Lack of trends across demographic subgroups in combined rates adding these subtypes**
 - Supportive of misclassification of all these selected subtypes over time



Results: 3- Path report QC



Results: Dx/classification issues

- 165 of 286 eligible NOS cases (58%)
- Representative series
- No difference from the 121 not reviewed by
 - age (four groups, $p=0.11$)
 - gender ($p=0.21$)
 - race/ethnicity ($p=0.22$)
 - tumor site ($p=0.55$)
 - disease stage ($p=0.37$)



Results: Dx/classification issues

- Among 165 reviewed NOS cases
 - 88 (53%) mentioned choice of NOS classification
 - NOS classification justified for 20/88 (23%)
 - Biopsy “insufficient” for subtyping for 21/88 (24%)
 - Core/FNA biopsies used in 121/165 (73%)
 - 20/21 (95%) cases with “insufficient” specimen
 - Specific histology subtype w/o SEER-approved terminology for 14/165 (9%)
 - Coding error for 32/165 (19%)
 - Specific HL histologic subtypes missed for 27 (84%)
 - Another cancer dx missed for 5 (16%)
 - 4 NHL, 1 neuroendocrine tumor



Summary: 3-Dx/classification issues

- QC review of NOS epath reports
 - Documented contributing pathology practices
 - Majority use of non-excisional biopsies
 - Insufficient biopsy specimens for histologic diagnosis
 - Coding errors



Discussion: Explanations?



Trends from risk factor change?

- NS
 - Risk with environments → early-life social isolation
 - “Protective” effect of preschool attendance
 - ↑ % children in daycare or preschool
 - 8%, 15%, 20%, 30%, 31%, 28%, and 35% in 1965, 1977, 1982, 1984-85, 1988, 1991 and 1993
 - Consistent with declines in NS rates in adolescents and young adults



Trends from risk factor change?

- MC

- Cigarette smoking prevalence: decrease?
- Lower SES: SES increase?
 - *However, few major changes over study period*
- HIV infection: decrease?
 - HIV infections ↑ since 1992 but then stabilized
 - Antiretroviral rx in mid-1990s ↓ MC risk
 - *However:*
 - *Observed MC rate ↓ across gender*
 - *Only 10% of male MC = HIV-positive*
 - *Same results in California data (38% of all study cases) with or without HIV cases*



Trends from artifact?

- **Diagnostic practice**
 - Core needle biopsies, FNA in place of excisional bx
 - Smaller quantity and lower quality of tumor tissue
 - Tissue-preserving tumor architecture
 - *Consistent with poorer diagnostic specificity*
 - Problem more prevalent for MC than NS
 - NS morphology often retained in needle bx
 - Except for NS 9664, more like MC
 - *Consistent with histologic subtype difference*
 - Uptake of new biopsy methods over time
 - *Consistent with ↓ ability to diagnose MC (and LD) and ↑ use of NOS classification*



Trends from artifact

- **Classification practice**
 - No clinical implication of histologic subtypes
 - WHO classification interpreted as requiring
 - Only distinction between cHL and nLP
 - No need for specific histologic subtypes
 - cHL is coded as NOS 9650
 - *Half of reviewed NOS diagnoses recorded without further comment*
 - Consistent but not definitive
 - For NS 9665-9667, exclusion from WHO classification in 2008



Implications



Implications of ↓ subtyping

- For epidemiology
 - Histology-specific rates difficult to interpret
 - Confounds secular trends
 - NOS must be included as “subtype” in HL research
 - *Now the second most common cHL category*
- For etiology
 - ↓ ongoing evaluation of subtype differences found in
 - Gene expression profiling
 - Transcriptional analyses of HL malignant cells
- For clinical medicine
 - Survival varies markedly by histologic subtype
 - Therapies for subtypes with poorer outcomes



Recommendations

- Increased use of histology subtype classification!
- Pathology practice
 - Use excisional biopsies as first choice for initial dx
 - National Comprehensive Cancer Network guideline
 - Use less invasive biopsy techniques for
 - e.g., screening (i.e., to rule out malignancy), follow-up biopsies, deep HL lesions, clinical contraindication to open biopsy
- Cancer registry practice
 - ↑ QC at central registries
 - In CA, state budget-driven ↓ in QC practices (visual editing)



Conclusions

- HL histologic subtyping diminishing
 - Despite well-recognized importance of histologic subtype heterogeneity
- Affects future HL research
 - Surveillance studies
 - Epidemiologic research (incidence, outcomes)
 - Research into Rx targeted to reduce survival disparities across subtypes
- *Increase accuracy of cHL histologic subtyping*
 - Adhering to current biopsy best practices
 - Improving registry QC of lymphoma subtype coding



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