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Cancer Surveillance Series: Non-Hodgkin's Lymphoma Incidence by Histologic Subtype in the United States From 1978 Through 1995

Frank D. Groves, Martha S. Linet, Lois B. Travis, Susan S. Devesa

Background: Clinical investigations have shown prognostic heterogeneity within the non-Hodgkin's lymphomas (NHLs) according to histology, but few descriptive studies have considered NHLs by subgroup. Our purpose is to assess the demographic patterns and any notable increases in population-based rates of different histologic subgroups of NHL. **Methods:** Using data collected by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, we calculated incidence rates for the major clinicopathologic categories of NHL by age, race, sex, geographic area, and time period. **Results:** Among the 60 057 NHL cases diagnosed during the period from 1978 through 1995, total incidence (per 100 000 person-years) was 17.1 and 11.5 among white males and females, respectively, and 12.6 and 7.4 among black males and females, respectively. However, rates for follicular NHLs were two to three times greater among whites than among blacks, with little sex variation. Blacks demonstrated much higher incidence than whites for peripheral T-cell NHL, with the incidence rates higher in males than in females. For other NHL subgroups, the incidence rates for persons less than 60 years of age were generally higher among males than among females, with little racial difference; at older ages, the rates were higher among whites than among blacks, with little sex difference. High-grade NHL was the most rapidly rising subtype, particularly among males. Follicular NHL increased more rapidly in black males than in the other three race/sex groups. Overall, the broad categories of small lymphocytic, follicular, diffuse, high-grade, and peripheral T-cell NHL emerged as distinct entities with specific age, sex, racial, temporal, and geographic variations in rates. **Conclusions:** Findings from our large, population-based study reveal differing demographic patterns and incidence trends according to histologic group. Future descriptive and analytic investigations should evaluate NHL risks according to subtype, as defined by histology and new classification criteria. [J Natl Cancer Inst 2000;92:1240-51]

With an estimated 54 900 new cases projected for the year 2000 in the United States (1), non-Hodgkin's lymphoma (NHL) is now the fifth most common malignant neoplasm after cancers of the breast, prostate, lung, and colon. Although NHL incidence and mortality rates worldwide have risen rapidly during the past few decades (2-4), the reasons for these increases are largely unknown. While risk factors for selected types of NHL have been identified, etiologic influences for most types of NHL are unknown.

There are few comprehensive evaluations of the descriptive epidemiology of NHL that take subtype into account. These types of studies have been limited by the rarity of many NHL subtypes, the lack of a large, population-based incident case

group identified over a long interval and categorized according to a standardized approach, and problems with reproducibility of NHL classification as documented in population-based and clinical settings. Using the Iowa Surveillance, Epidemiology, and End Results (SEER)¹ Program registry data, researchers found 57%-63% agreement among expert pathologists in classifying NHL cases according to the Working Formulation (WF) (5) and 77% agreement among SEER Program coders in assigning the International Classification of Diseases for Oncology (ICD-O) codes to cases (6). Investigators from the Eastern Cooperative Oncology Group were unable to classify 4.3% of the NHL cases using WF categories but found similar levels of agreement (61%) among expert pathologists (7) as did Dick et al. (5).

While recognizing these limitations, we exploited a singular opportunity to examine the patterns and trends of NHL subtypes in a large population according to a standardized classification scheme.

METHODS

Ascertainment of Cases

The SEER Program of the National Cancer Institute has compiled incidence data since 1973 from population-based cancer registries in five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and in four metropolitan areas (Atlanta, GA; Detroit, MI; San Francisco, CA; and Seattle, WA) that make up approximately 10% of the U.S. population (8). Data routinely collected by participating cancer registries include anatomic site and histology of cancer as well as patient demographic characteristics, such as age, sex, race, and vital status.

Classification of Cases

Each SEER registry codes all cancers, including NHL, according to a standard classification scheme by use of information from diagnostic pathology reports in medical records. NHL cases diagnosed from 1973 through 1977 were classified according to the *Manual of Tumor Nomenclature and Coding* (MOTNAC) (9). Beginning in 1978, the more detailed scheme of the ICD-O (10) was adopted to code all NHLs and other cancers registered by the SEER Program. Since 1992, the SEER Program has coded NHL and other newly diagnosed cancers using the ICD-O, 2nd Edition (ICD-O-2) (11). The SEER Program used a computerized algorithm to recode the incident cancers diagnosed before 1992 according to ICD-O-2. Since the NHL categories used in MOTNAC were too few and too vague for precise classification, our analysis begins with cases initially diagnosed in 1978, the first year ICD-O was used, and includes 60 057 cases diagnosed through 1995, the most recent available year.

The SEER Program also has used the ICD-O-2 morphology codes to recategorize the NHL cases according to the WF, an NHL classification scheme developed for prognostic purposes (12). There are 10 subtypes (designated A-J)

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See "Notes" following "References."

in the WF; based on differences in survival, these have been designated as low grade (subtypes A–C), intermediate grade (subtypes D–G), and high grade (subtypes H–J). Overlaid on this clinical grading scheme is the morphologic distinction among the follicular (B–D), diffuse (E–G), and high-grade (H–J) subtypes. Most ICD-O-2 designations correspond to one of the 10 subtypes (13), although several ICD-O-2 categories, such as follicular, NOS (not otherwise specified), diffuse, NOS, and high-grade, NOS, are insufficiently precise to allow for detailed classification using A–J. Therefore, we combined these categories with the 10 WF subtypes to derive six major types, as shown in Table 1: small lymphocytic NHL, follicular NHL, diffuse NHL, high-grade NHL, peripheral T-cell NHL, and NHL, NOS.

Calculation and Presentation of Rates

Subtype-specific NHL incidence rates were calculated for population subgroups according to age, sex, and race, as well as registry and time period. Age-specific rates were calculated for 18 5-year age groups, expressed as new cases per 100 000 person-years, and then directly age-adjusted to the 1970 U.S. standard population. Age-adjusted, age-specific incidence rates were also ascertained for eight broader age groups (0–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, and ≥75 years).

The figures are presented using uniform semilogarithmic scales so that rates of change can be compared (14). Percent increases for total NHL and for each subtype were calculated by comparing the rates for three 6-year time periods: from 1978 through 1983, from 1984 through 1989, and from 1990 through 1995. For all extranodal NHL cases, we examined incidence by anatomic site of origin and histologic subtype over the entire 18-year period because of the rarity of NHL in many of the extranodal categories. The distribution of NHL cases classified by immunophenotype (B cell versus T cell versus other and unspecified immunophenotypes) was evaluated for the period from 1990 through 1995, since the proportion of NHL cases with immunophenotype recorded in the SEER files before 1990 was small.

Statistical Considerations and Comparisons of Rates

This study represents a descriptive exploratory analysis looking for patterns, without any *a priori* hypotheses. The variance of an incidence or mortality rate can be approximated by dividing the rate (number of new cases or deaths/100 000 person-years) squared by the number of events (number of new cases or deaths, respectively) on which the rate was based. Differences in rates and ratios of rates can be tested by calculating approximate confidence intervals (CIs) according to (15). If c = the number of cases, p = the number of people in the population, and the rate $r = c/p$, then the 95% CI for the rate is $r \pm 1.96 * SQRT[var(r)] = r \pm 1.96 * r/SQRT[c]$; the 95% CI for a rate difference is $(r1 - r2) \pm 1.96 * SQRT[var(r1) + var(r2)] = (r1 - r2) \pm 1.96 * SQRT[r1*c1/c1 + r2*c2/c2]$; and the 95% CI for a rate ratio is $\exp[\ln(r1/r2) \pm 1.96 * SQRT(1/c1 + 1/c2)]$.

RESULTS

Age-Adjusted Incidence Rates by Subtype, Race, and Sex

During the period from 1978 through 1995, 60 057 cases of NHL were diagnosed among residents of the nine SEER areas: 53 171 among whites, 3584 among blacks, 2831 among persons of other specified races (2226 Asians, 232 Hawaiians, 138 American Indians or Alaska Natives, 31 Pacific Islanders, and 204 others), and 471 among persons of unknown race. Incidence rates for blacks and whites are shown in Table 2; incidence rates for persons of other races are not included because of small numbers of cases and difficulties in estimating intercensal population denominators.

Across all four race/sex groups, diffuse NHL accounted for 39%–44% of NHL, and small lymphocytic NHL accounted for 9%–10%. The proportion of NOS cases was lower among whites (14% for males and 13% for females) than among blacks (20% for males and 18% for females). The total NHL rates were 40%–70% higher among whites than among blacks and among males than among females. The male-to-female incidence rate ratios were greater than 2 for high-grade and peripheral T-cell NHL and greater than 1 for most other histologic types, but they were close to unity for follicular NHL among whites. The white-to-black incidence rate ratios were around 2–3 for follicular NHL and ranged between 1 and 2 for most other major types but were less than 1 for peripheral T-cell NHL.

Age-Specific Incidence Rates

Total NHL incidence rates (Fig. 1) increased monotonically with age in all race and sex subgroups. No racial differences were observed in the age-specific incidence curves until age 45 years for males and age 35 years for females; after these ages, the rates were higher in whites than in blacks. Age-specific incidence rates were higher in males than in females at all ages, regardless of race. Rates for NHL, NOS, increased with age, with higher rates among blacks than among whites for ages 15–64 years among males and for ages 15–54 years among females; rates were notably higher among males than among females for ages 15–64 years and, subsequently, there was little

Table 1. Classification of non-Hodgkin's lymphoma*

Major types	Working Formulation subtypes	ICD-O-2 codes
Small lymphocytic	A: Small lymphocytic	9670, 9671
Follicular	B: Follicular small	9693, 9694, 9695, 9696
	C: Follicular mixed	9691, 9692
	D: Follicular large	9697, 9698
	(Follicular, NOS)†	9690
Diffuse	E: Diffuse small	9672, 9673, 9674
	F: Diffuse mixed	9675, 9676
	G: Diffuse large	9593, 9680, 9681, 9682, 9683
	(Diffuse, NOS)†	9595, 9677, 9688, 9710, 9711, 9715
High-grade	H: Immunoblastic	9684
	I: Lymphoblastic	9685
	J: Small noncleaved	9686, 9687
	(High-grade, NOS)†	9594
Peripheral T-cell		9700, 9701, 9702, 9703, 9704, 9705, 9706, 9707, 9708, 9709, 9712, 9713, 9714
NOS		9590, 9591, 9592

*ICD-O-2 = International Classification of Diseases for Oncology, 2nd edition (11); NOS = not otherwise specified.

†Subtypes within parentheses were not categorized to a specific subtype A–J but were included in the respective major type.

Table 2. Non-Hodgkin's lymphoma cases and incidence rates* in nine SEER areas (from 1978 through 1995) by race, sex, and histology†

Histology	White males		White females		Black males		Black females		Rate ratios			
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	White males/ white females	Black males/ black females	White males/ black males	White females/ black females
	Total	28 635	17.1	24 536	11.5	2114	12.6	1470	7.4	1.5	1.7	1.4
Small lymphocytic												
A: Small lymphocytic	2617	1.6	2342	1.1	205	1.4	148	0.8	1.5	1.8	1.1	1.4
Follicular	4969	3.0	5451	2.7	205	1.3	176	0.9	1.1	1.5	2.3	3.1
B: Follicular small	2591	1.6	2685	1.3	93	0.6	72	0.4	1.2	1.6	2.6	3.6
C: Follicular mixed	1307	0.8	1582	0.8	48	0.3	54	0.3	1.0	1.1	2.5	2.9
D: Follicular large	642	0.4	751	0.4	38	0.2	26	0.1	1.1	1.6	1.7	2.6
(Follicular, NOS)‡	429	0.3	433	0.2	26	0.2	24	0.1	1.2	1.5	1.6	1.9
Diffuse	12 157	7.3	10 930	5.0	831	5.1	623	3.2	1.4	1.6	1.4	1.6
E: Diffuse small	2365	1.5	1975	0.9	146	1.0	126	0.7	1.6	1.5	1.5	1.4
F: Diffuse mixed	1472	0.9	1512	0.7	111	0.7	98	0.5	1.3	1.4	1.3	1.4
G: Diffuse large	8133	4.8	7291	3.4	562	3.3	391	1.9	1.4	1.7	1.5	1.7
(Diffuse, NOS)‡	187	0.1	152	0.1	12	0.1	8	0.0	1.6	2.0	1.4	1.8
High-grade	3408	2.0	1776	0.9	278	1.5	129	0.6	2.3	2.3	1.4	1.3
H: Immunoblastic	1825	1.0	1121	0.5	148	0.8	88	0.4	2.0	1.9	1.3	1.2
I: Lymphoblastic	377	0.2	173	0.1	43	0.2	15	0.1	2.6	2.7	1.2	1.3
J: Small noncleaved	1183	0.7	462	0.2	84	0.4	25	0.1	3.1	3.4	1.8	1.9
(High-grade, NOS)‡	23	0.0	20	0.0	3	0.0	1	0.0	1.0	2.0	0.5	1.0
Peripheral T-cell	1346	0.8	784	0.4	168	1.1	126	0.6	2.1	1.8	0.8	0.6
NOS	4138	2.4	3253	1.4	427	2.4	268	1.3	1.7	1.8	1.0	1.1

*All rates are per 100 000 person-years at-risk, age-adjusted to the 1970 U.S. population.

†SEER = Surveillance, Epidemiology, and End Results Program; NOS = not otherwise specified.

‡Subtypes within parentheses were not categorized to a specific subtype A–J but were included in the respective major type.

difference in rates according to sex among persons aged 65 years or older.

Peripheral T-cell NHL increased with age and was more common among blacks than among whites at almost all ages, although the male excess among blacks became apparent only after the age of 35 years. Small lymphocytic NHL rates increased exponentially with age to reach more than 100-fold greater for all whites over the age of 75 years than for those aged 25–34 years, and the rates showed little racial disparity. For follicular NHL and for its subtypes, rates rose with age, although sex differences were small, and whites of both sexes had higher rates than blacks at most ages.

Diffuse NHL rates increased with age but varied little between the races among the middle-aged groups; rates were higher among whites at older ages. High-grade NHL was the only type to occur notably among children. The excess in males of high-grade NHL, mostly small noncleaved NHL, was particularly marked under the age of 50 years; no consistent racial disparity was evident. In contrast to the more rapid rise in incidence occurring with increasing age for all other subtypes of NHL, the age-specific incidence of small noncleaved NHL increased relatively slowly with age, and lymphoblastic NHL actually showed a “U-shaped” age-specific incidence curve. (High-grade NHL rates by subtype among females were so low that they are not shown in Fig. 1.) Thus, similarities in the shapes of the age-specific incidence curves of the subtypes within each major type support the aggregation of the three follicular subtypes, the three diffuse subtypes, and the three high-grade subtypes.

Regional Variation in Age-Adjusted Incidence Rates Among Whites

Data presented (Table 3) are limited to whites because the numbers of NHL cases among blacks were too small to allow for

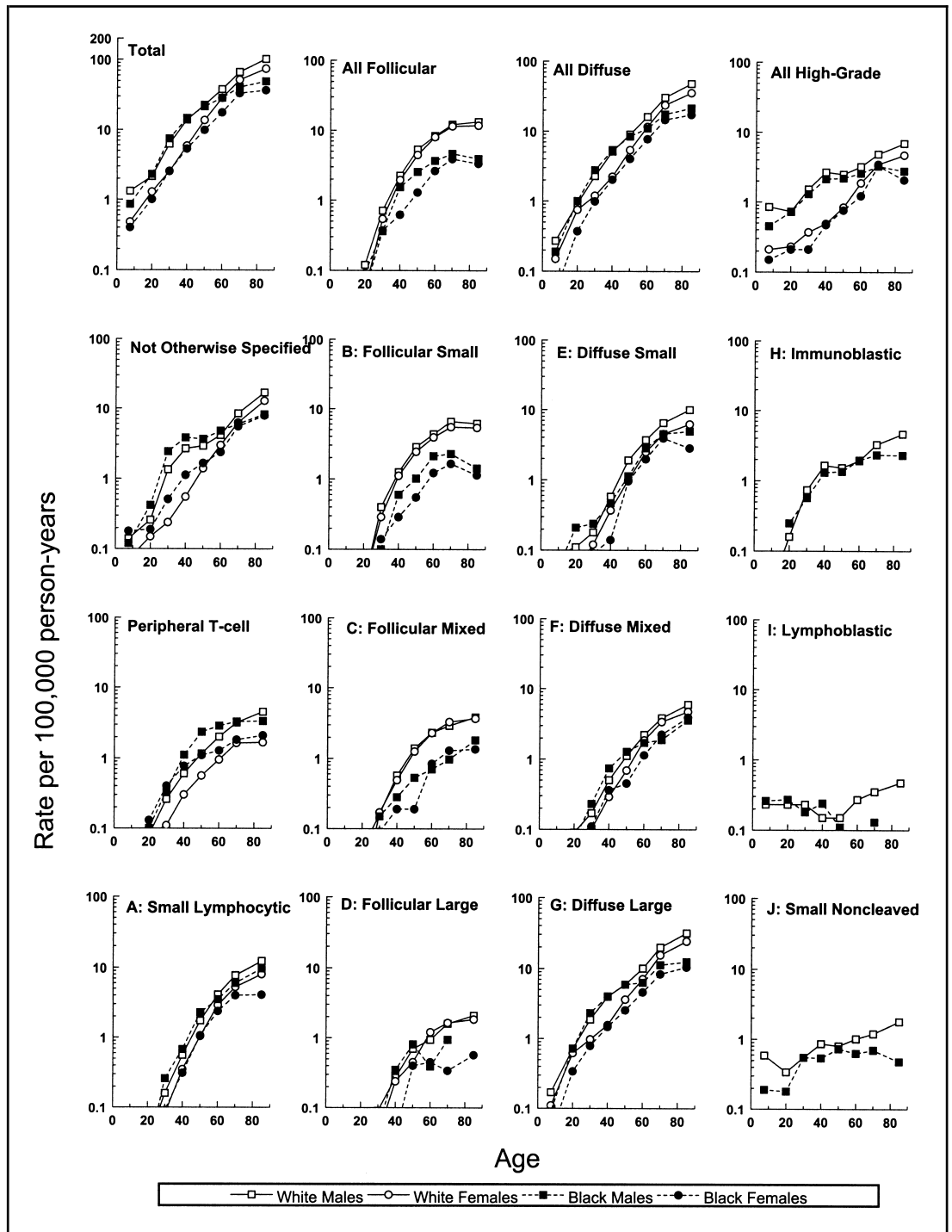
meaningful geographic comparisons. Among whites, the geographic patterns differ according to sex, and the registry-specific data are listed within sex in decreasing order of total NHL rate. For males, age-adjusted incidence rates in San Francisco were higher than the SEER rates for total NHL and for every major subtype except small lymphocytic NHL. Rates in New Mexico were lower than the SEER rates for total NHL and for every major subtype as well. Male total NHL incidence rates were 82% higher in San Francisco than in New Mexico; the San Francisco excess was largely attributable to the elevated rates for diffuse NHL (76% higher in San Francisco than in New Mexico) and high-grade NHL (almost twice as high in San Francisco than in New Mexico).

Among females, age-adjusted incidence rates in both Detroit and Connecticut were higher than the SEER rates for total NHL and for high-grade NHL in Detroit and for small lymphocytic NHL in Connecticut, although these differences were small. Rates for females in New Mexico were lower than the SEER rates for total NHL and for the small lymphocytic, follicular, and diffuse subtypes. With total NHL incidence in Detroit being only 33% higher than in New Mexico, it is clear that there is less variation in NHL incidence among females than among males. In particular, the rates among white females in San Francisco were close to the SEER rates for most NHL subtypes, in contrast to the marked excesses observed there among white males.

Site Distribution of Extranodal Lymphomas by Subtype

Approximately 27% of all NHL cases were extranodal (Table 4); for most histologic groups, this fraction ranged between 21% and 33%, with two notable exceptions: 82% of peripheral T-cell NHL cases were extranodal, almost all of which involved the skin, and only 9% of follicular NHL cases were extranodal. Almost half of all extranodal NHL cases were of a diffuse his-

Fig. 1. Incidence rates for non-Hodgkin's lymphoma in the nine Surveillance, Epidemiology, and End Results areas for the period from 1978 through 1995 by age group 0-14, 15-24, 25-34, . . . , 65-74, greater than or equal to 75 years of age. *Note:* each rate was plotted at the mid-point of the age interval. Data were not shown for females in panels **I** and **J** because of small numbers and low rates.



tology. The majority of the NHLs arising from the following sites had a diffuse histologic pattern: stomach, small intestine, colon, soft tissue, thyroid, and testis. Most extranodal NHLs were concentrated in just four sites: skin, stomach, brain, and small intestine. About half of cerebral NHLs were of an unspecified histology.

Immunophenotype Distribution by Subtype

In recent years, the SEER Program has collected immunophenotypic data for NHL. Before 1990, fewer than one fourth of all NHL cases in the SEER database had immunophenotypic data recorded. Between 1990 and 1995, almost 61% of all NHL cases still were recorded as unknown immunophenotype, about

34% were B-cell type, and approximately 6% were T-cell type (Table 5). During the period from 1990 through 1995, the proportion of cases not specified as T or B cell ranged by subtype from 36% to 100%. The percentage of NHL cases of unknown phenotypic type decreased from 68% in 1990 to 53% in 1995.

Trends in Incidence of NHL

During the period from 1978-1983 to 1990-1995, age-adjusted total NHL incidence rates (Fig. 2) increased by 77% in black males and by 53% in white males but only by 39% and 33% among black and white females, respectively. When a more detailed evaluation was conducted to compare the change in incidence among three time periods (1978-1983, 1984-1989,

Table 3. Non-Hodgkin's lymphoma cases and incidence rates* among whites (from 1978 through 1995) by histology and SEER area†

Sex and registry‡	No. of cases	Incidence rates							% NOS of total
		Total§	Small lymphocytic	Follicular	Diffuse	High-grade	Peripheral T-cell	NOS	
Males									
San Francisco–Oakland (CA)	5700	22.2	1.6	3.4	9.0	3.4	1.2	3.7	16.5
Seattle–Puget Sound (WA)	4420	17.4	1.7	3.1	7.1	1.7	0.9	3.0	17.0
Metropolitan Detroit (MI)	4458	16.8	1.8	3.0	6.9	1.7	0.8	2.6	15.5
Connecticut	4610	16.5	1.8	2.7	7.0	1.8	0.9	2.3	13.8
Hawaii	418	16.3	1.2	2.6	6.9	3.2	0.4	2.0	12.5
Iowa	4368	16.2	1.6	3.6	7.9	1.3	0.6	1.2	7.6
Metropolitan Atlanta (GA)	1689	15.7	1.6	2.7	7.2	1.7	0.7	1.7	10.9
Utah	1628	14.8	1.4	2.2	6.3	2.2	0.5	2.2	15.2
New Mexico	1344	12.2	0.9	2.4	5.1	1.7	0.6	1.6	13.1
Nine SEER areas	28 635	17.1	1.6	3.0	7.3	2.0	0.8	2.4	14.1
Females									
Metropolitan Detroit	4212	12.1	1.1	2.9	5.0	1.0	0.4	1.8	14.5
Connecticut	4483	12.0	1.2	2.6	5.1	1.0	0.4	1.7	13.9
Iowa	4349	11.8	1.0	3.0	6.0	0.7	0.3	0.8	6.9
San Francisco–Oakland	3685	11.8	1.1	2.8	5.1	0.9	0.6	1.3	10.9
Seattle–Puget Sound	3512	11.3	1.0	2.8	4.8	0.7	0.4	1.7	14.7
Metropolitan Atlanta	1477	11.0	1.1	2.6	5.0	0.7	0.3	1.3	11.5
Utah	1376	10.5	0.9	1.9	4.6	1.0	0.4	1.8	16.7
Hawaii	244	10.0	1.1	2.5	4.2	1.0	0.3	0.9	9.2
New Mexico	1198	9.1	0.8	2.1	3.6	1.0	0.3	1.4	14.8
Nine SEER areas	24 536	11.5	1.1	2.7	5.0	0.9	0.4	1.4	12.5

*All rates are per 100 000 person-years at-risk, age-adjusted to the 1970 U.S. population.

†SEER = Surveillance, Epidemiology, and End Results Program; NOS = not otherwise specified.

‡Registries listed within sex in decreasing order of total rate.

§Because of rounding, the total rate may not equal the sum of the subtype rates.

Table 4. Non-Hodgkin's lymphoma cases and incidence rates* (all races and both sexes) in nine SEER areas (from 1978 through 1995) by histology and site†

Site	No. of cases	Incidence rates						
		Total‡	Small lymphocytic	Follicular	Diffuse	High-grade	Peripheral T-cell	NOS
All sites	60 057	13.5	1.3	2.6	5.8	1.4	0.6	1.9
Nodal	43 677	9.9	1.0	2.4	4.2	1.0	0.1	1.3
Extranodal	16 380	3.7	0.3	0.2	1.7	0.4	0.5	0.6
Skin	2969	0.7	<0.1	<0.1	0.1	<0.1	0.5	0.1
Stomach	2717	0.6	0.1	<0.1	0.4	<0.1	<0.1	0.1
Brain	1569	0.3	<0.1	<0.1	0.1	0.1	<0.1	0.2
Small intestine	1185	0.3	<0.1	<0.1	0.1	0.1	<0.1	<0.1
Lung	647	0.1	<0.1	<0.1	0.1	<0.1	<0.1	<0.1
Soft tissue	639	0.1	<0.1	<0.1	0.1	<0.1	<0.1	<0.1
Colon	596	0.1	<0.1	<0.1	0.1	<0.1	<0.1	<0.1
Eye	534	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Thyroid	502	0.1	<0.1	<0.1	0.1	<0.1	<0.1	<0.1
All other sites	5022	1.1	0.1	0.1	0.6	0.1	<0.1	0.2

*All rates are per 100 000 person-years at-risk, age-adjusted to the 1970 U.S. population. *Note:* No rates were based on zero cases.

†SEER = Surveillance, Epidemiology, and End Results Program; NOS = not otherwise specified.

‡Because of rounding, the total rate may not equal the sum of the subtype rates.

and 1990–1995), the percentage increase slowed from 32% (from 1978–1983 to 1984–1989) to 16% (from 1984–1989 to 1990–1995) among white males, from 20% to 11% among white females, and from 19% to 17% among black females; only among black males did the percentage increase accelerate, from 21% to 46%.

High-grade NHL increased most rapidly between 1978–1983

and 1990–1995, tripling among males and doubling among females. Immunoblastic NHL was the fastest-growing high-grade subtype, followed by small noncleaved and lymphoblastic NHL (in that order). Other histologic types increased more slowly. Small lymphocytic NHL increased by 36%–44% in all four race/sex groups. Follicular NHL remained stable among black females and increased only 16%–22% among whites from 1978 to

Table 5. Non-Hodgkin's lymphoma cases (all races and both sexes) in nine SEER areas (from 1990 through 1995) by immunophenotype and histology*

Histology	No. of cases	Immunophenotype		
		T cell, %	B cell, %	Not specified T or B, %
Total	25 364	5.7	33.7	60.6
Small lymphocytic				
A: Small lymphocytic	2217	1.1	30.1	68.8
Follicular	4356	0.6	32.4	67.0
B: Follicular small	1948	0.5	30.2	69.4
C: Follicular mixed	1399	0.6	31.0	68.4
D: Follicular large	712	1.0	39.8	59.3
(Follicular, NOS)†	297	1.4	35.7	63.0
Diffuse	10 452	4.6	40.5	54.9
E: Diffuse small	1345	1.0	31.3	67.7
F: Diffuse mixed	1102	11.3	30.0	58.7
G: Diffuse large	7677	4.3	43.1	52.7
(Diffuse, NOS)†	328	4.0	52.3	43.3
High-grade				
H: Immunoblastic	1861	7.1	41.1	51.9
I: Lymphoblastic	253	43.9	19.8	36.4
J: Small noncleaved	788	1.0	37.9	61.0
(High-grade, NOS)†	2	0.0	0.0	100.0
Peripheral T-cell	1310	38.1	6.3	55.6
NOS	4125	3.7	25.5	70.8

*SEER = Surveillance, Epidemiology, and End Results Program; NOS = not otherwise specified.

†Subtypes within parentheses were not categorized to a specific subtype A–J but were included in the respective major type.

1995 but increased among black males by 25% between 1978–1983 and 1984–1989, followed by an even larger increase of 42% between 1984–1989 and 1990–1995, for a total increase of 77%. Diffuse NHL rose by 30%–41% among males versus 19%–25% among females, with the greatest increase (50%–91%) seen for diffuse large NHL. Diffuse small NHL was the only subtype that declined (42%–47%) in all four race/sex groups. Although incidence rates for peripheral T-cell NHL remained higher among blacks than among whites, the rate of increase was greater among whites (134%–161%) than among blacks (52%–84%), narrowing the racial gap. NHL, NOS, increased faster among males (128%–160%) than among females (42%–73%), with little difference by race within sex.

DISCUSSION

Our study is distinct in analyzing more than 60 000 NHL cases from a well-defined population simultaneously by age, sex, race, and histologic type, as well as by geographic area and time period of diagnosis. Major histologic categories of NHL differ in key characteristics. Follicular NHL is twice as common in whites as in blacks, but the male/female ratio is close to unity; however, the disproportionately rapid increase from 1978 through 1995 among black males has tended to increase the male/female ratio among blacks while reducing the white/black ratio among males. Diffuse NHL occurs more frequently among males than among females at middle ages and among whites than among blacks at older ages. Diffuse NHL accounts for close to half of the extranodal NHL, arising in the stomach, small intestine, colon, soft tissue, and thyroid. The incidence of high-grade NHL tripled among males and doubled among females from 1978 through 1995. High-grade and peripheral T-cell NHL

are both twice as common in males as in females. Peripheral T-cell accounts for 5%–10% of NHL in all age groups and is unique among subtypes in being more common among blacks than among whites. The subtype-specific NHL incidence patterns may reflect the influence of different etiologic as well as host factors as summarized below.

Risk Factors Related to Functional Immunologic Abnormalities

NHL is a malignancy of lymphocytes, the primary effector cells of the immune system. Disorders characterized by severe immunologic compromise or even moderately serious immune dysfunction have been consistently linked with excesses of NHL (*see below*). Conversely, selected exposures that may be associated with low-to-moderate immune effects, such as infections, vaccinations, allergies, medications, and other influences, may be inversely associated with NHL risk (16,17).

Therapeutic immunosuppression. Increased rates of NHL have been described in a clinical series of patients treated with immunosuppressive drugs following transplantation with donor kidneys (35- to 59-fold) (18–20) or heart or bone marrow (68- to 336-fold) (21,22). The cumulative incidence of NHL, however, is only about 1% 10 years after bone marrow transplantation (23). NHL after solid organ transplants tends to be of diffuse large or immunoblastic histology (24), and extranodal involvement is common (25). Despite the dramatic increase from 12 788 organ transplants in the United States in 1988 to 20 354 in 1996 (26), transplant-associated NHL accounts for a minuscule fraction of this malignancy.

Autoimmunity. Relative risks ranging from 2 to 44 for NHL have been observed in patients with celiac disease or dermatitis herpetiformis (27,28), systemic lupus erythematosus (29,30), sicca syndrome (31,32), and rheumatoid arthritis (33–38), with lower risks in population-based studies (30,37,38), although data on histologic type of NHL are limited. NHL-related autoimmune diseases are unlikely to contribute meaningfully to rising secular trends in NHL, since the incidence of autoimmune disorders has either not increased (39) or risen only modestly (40) over time.

Congenital immunodeficiency. Data from the Immunodeficiency Cancer Registry (41) are consistent with notably increased risks of NHL among children with congenital X-linked immunodeficiency and severe combined system immunodeficiency, as well as with excesses in young persons with ataxia-telangiectasia or Wiskott–Aldrich syndrome. The rarity of congenital immunodeficiency disorders, however, precludes a substantial contribution to the increasing incidence of NHL, and subtypes of lymphoma have not been described systematically.

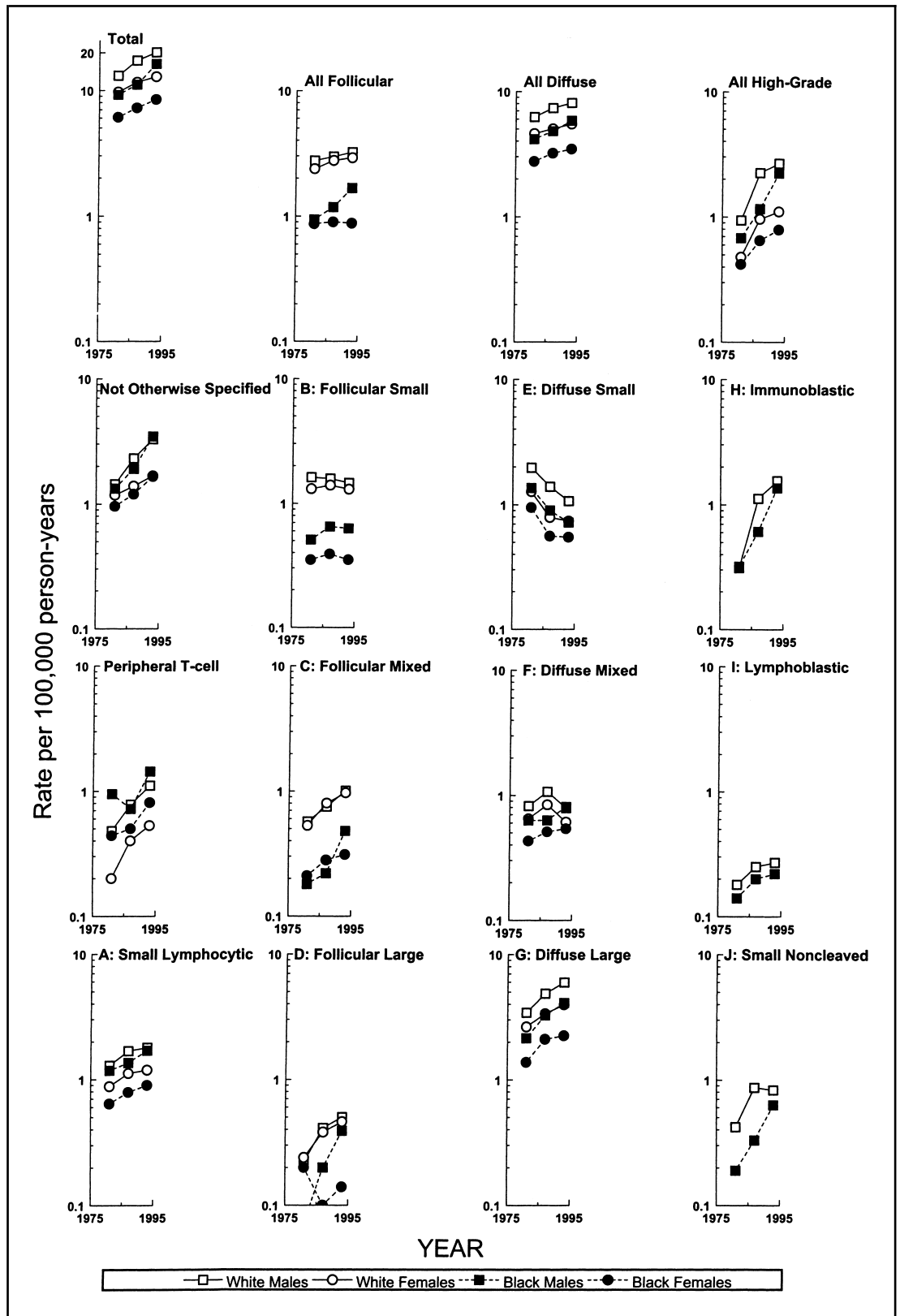
Specific Infectious Agents

Certain infectious agents, which either precede or occur concomitantly with various immune-related conditions associated with NHL, may be etiologically important.

Human immunodeficiency virus (HIV) infection. Patients with acquired immunodeficiency secondary to HIV infection are at 59- to 104-fold risk of NHL (42,43). The cumulative incidence of NHL in HIV-infected subjects receiving antiretroviral therapy was 29% after 36 months (44). Among HIV-related NHL, high-grade B-cell subtypes predominate (45), especially immunoblastic and Burkitt's (small noncleaved) NHL (42), although diffuse subtypes also occur (43).

The excess of high-grade NHL in San Francisco, particularly

Fig. 2. Trends in age-adjusted (U.S. population, 1970) incidence rates for non-Hodgkin's lymphoma in nine Surveillance, Epidemiology, and End Results areas (from 1978–1983 through 1990–1995).



among unmarried white males, probably reflects the burden of HIV infection (46), although incidence rates were elevated in San Francisco whites of both sexes in earlier national cancer surveys conducted during 1947–1948 (47) and 1969–1971 (48). Acquired immunodeficiency syndrome (AIDS) accounts for a relatively small fraction of NHL, however, in the total geographic regions covered by the SEER registries (17,46,49).

Hepatitis C virus (HCV) infection. Findings of a relation between HCV and NHL are mixed. Associations of HCV with B-cell NHL (50) and with follicular and gastric mucosa-associated lymphoid tissue (MALT) NHL (51), but not with intermediate- or high-grade NHL (52), have been reported in some studies. A nationwide survey from 1988 through 1994 estimated 1.8% seroprevalence of HCV, higher in males than in

females and in non-Hispanic blacks than in whites (53). The etiologic role of HCV in NHL, however, is not yet well established.

Human T-lymphotropic virus (HTLV) types I/II. Infection with HTLV-I, especially in early childhood, is associated with subsequent excesses of peripheral T-cell NHL in southeastern Japan and in the Caribbean (54–56), but this retrovirus causes only about 10% of mycosis fungoides and Sézary syndrome in the United States (57,58). Combined HTLV-I/II infections are also exceedingly rare in the United States, with seroprevalence ranging from 0.03% to 4.2% in military service applicants (59), blood donors (60,61), forensic autopsy subjects (62), and emergency room and clinic patient populations (63,64). U.S. intravenous drug users make up a small fraction of the population, so even though 25% of them are infected with HTLV-I/II (65–67), they would have a negligible effect on NHL rates.

Helicobacter pylori. Although primary gastric lymphomas are mostly high-grade NHL, low-grade B-cell MALT gastric lymphomas are frequently preceded by unrecognized infection with *H. pylori* (68). Eradication of the infection in early-stage NHL can result in tumor regression (68).

Epstein-Barr virus (EBV). Post-transplant lymphoproliferative disorders (PTLDs) developing within 6 months as clinically aggressive lymphomas of donor cell origin and NHL among AIDS patients are thought to result from uncontrolled proliferation of EBV-transformed B lymphocytes in the setting of immune dysfunction (23,69–72). The PTLDs include plasmacytic hyperplasias, polymorphic lymphoproliferative disorders, and frank malignant lymphomas (72). Primary immunodeficiency disorders such as X-linked lymphoproliferative disease may also first become manifest after EBV infection (73). Burkitt's (small noncleaved) lymphoma in Africa is a distinct entity arising among children in a defined geographic belt (74). Early EBV infection has been consistently associated with African Burkitt's lymphoma on the basis of epidemiologic, serologic, and molecular studies (73). Malaria has been identified as a cofactor based on the overlapping geographic distribution, the high rates in the same population, and reduction in both after chloroquine prophylaxis (73).

In the United States, the rarity of HTLV-I, the declining prevalence of *H. pylori* (75), and the ubiquity of EBV infection suggest that these agents are unlikely to explain the increases in NHL.

Blood Transfusions

Blood transfusions, which may transmit infectious agents and other immune-modulating antigenic exposures, have not been associated with NHL in a large Swedish cohort (76) or in two U.S. studies (77,78). Thus, there is little evidence that the dramatic rise in blood transfusions in the last five decades (79,80) contributed to the rising rates of NHL.

Agricultural and Pesticide Exposures

NHL has been linked with exposure to pesticides, crops, and livestock. Italian farmers and animal breeders were found to have twofold risks of low-grade NHL (81), and U.S. farmers had a twofold risk of lymphocytic NHL (82). A U.S. population-based, case-control study found small excesses of follicular NHL among meat packaging and processing workers (83).

The use of agricultural herbicides (particularly 2,4-

dichlorophenoxyacetic acid) was associated with a notable dose-response effect for NHL, particularly among farmers who mixed and applied the compounds themselves (84). Herbicides increased the risk of follicular large-cell NHL in Nebraska (85), whereas modest increases for small lymphocytic (associated with certain crops and pesticide categories) and diffuse (linked with specific herbicides and pesticides) NHL occurred among farmers in Iowa and Minnesota (86). Total U.S. pesticide use rose from 647 million pounds in 1964 to 1144 million pounds in 1979 and then declined to 973 million pounds in 1995 (87). The role of agricultural and residential pesticides in the etiology of NHL requires further evaluation. The relatively small numbers of agricultural, lawn care, and pesticide manufacturing workers and pesticide applicators suggest that these workers account for only a modest fraction of the NHL increase in the general population.

Lifestyle Factors

Diet. Milk (88), red meat (89,90), and butter, liver, and ham (91) have been associated with increased risks of NHL, whereas fruit (particularly citrus) (88,89), carrots, and whole-grain dietary products (91) have been linked with reduced risks. In one study (90), risks rose with increasing estimated serum retinol levels and declined with increasing estimated β -carotene levels. High intake of red meat, *trans*-unsaturated fat, and saturated fat was also linked with increased risks in the Nurses' Health Study cohort (92).

Cigarette smoking. Most large cohort and case-control studies of cigarette smoking and cancer (93–95) have detected little effect of smoking on risk of NHL. Smoking was linked with high-grade NHL in several case-control studies (91,96,97) and with follicular NHL in a few cohort studies (98,99).

Hair dye. Findings are inconsistent, with small increases in incidence of follicular NHL (100) or NHL mortality (101) associated with hair dye use (particularly black or brown dyes used for ≥ 10 years) found in some but not in other (102,103) large cohort or case-control studies.

UV radiation. Spatial and temporal correlations in incidence rates for nonmelanoma skin cancer and NHL have been hypothesized to support a link between solar UV radiation (UVR) and NHL (104); the proposed mechanism involves an immunosuppressive effect of UVR. Swedish investigators (105) described increased risks of NHL and chronic lymphocytic leukemia subsequent to melanoma and nonmelanoma skin cancers and excesses of both types of skin cancer subsequent to NHL. In England and Wales, ambient solar UV levels have been correlated with NHL incidence (106), and women (but not men) in outdoor occupations were found to have an increased risk of NHL (107). Ecologic studies (108,109) have shown NHL to be inversely, although weakly, correlated with latitude in European but not in U.S. Caucasians. Analytic investigations would help to clarify whether solar UVR is associated with NHL.

Relatively few studies have addressed diet, smoking, or other lifestyle risk factors for NHL; the effect of these exposures on NHL risk, if any, has yet to be firmly established and seems unlikely to explain the increasing trends.

Genetic Factors

Yunis et al. (110) found 14;18 chromosomal translocations associated with follicular NHL, 8;14 translocations linked with Burkitt's lymphoma (classified here with small noncleaved

NHL), and trisomy 12 increased in small lymphocytic NHL. The q32 band on chromosome 14 is the most common breakpoint in NHL (111). The t(14;18) (q32;q21) translocation, involving the bcl-2 gene, occurs in 90% of follicular lymphomas (112) and in some patients with non-neoplastic lymphoproliferation (113). The increased chromosome breakages and rearrangements involving 14q32 and 18q21 observed in healthy pesticide fumigators have not yet been linked with NHL characterized by t(14;18) (q32;q21) translocations (114). The well-established, nonrandom cytogenetic translocations or other genetic lesions characterizing certain NHL subtypes may be associated with different etiologies but do not explain the increasing trends. Familial aggregation and the notable occurrence of various immunologic abnormalities among multiple-case family members with and without NHL or related lymphoproliferative neoplasms may reflect genetic factors and/or gene-environment interaction, but such familial occurrence does not account for the rising incidence (115).

Demographic and Temporal Variation in NHL Incidence

An earlier study (116) evaluated SEER Program NHL subtype-specific data (from 1973 through 1987) for all races combined. Our more detailed assessment, revealing important differences in age, sex, race, geographic, and recent trend patterns from 1978 through 1995, suggests differing etiologies of NHL subtypes. Data from the limited number of available analytic studies, however, do not consistently support subtype-specific variation in risk of NHL.

The onset of the rising NHL incidence is difficult to ascertain, although Connecticut Tumor Registry data have shown fourfold to sixfold increases in NHL since 1935 (117). Other U.S. NHL data are lacking before World War II, since NHL was first evaluated as a separate entity in the late 1940s (47) and was initially categorized only as lymphosarcoma or reticulosarcoma in the late 1960s (9,48).

In the consideration of patterns by histologic type, the potential impact of unclassified cases needs to be addressed. The proportion NOS was higher among blacks than among whites, which could reduce the true type-specific white/black rate ratios (Table 2), but the general patterns observed are most likely real. The higher NOS rates among middle-aged than among older persons (Fig. 1) and the notably higher rates among males than among females may suggest that these NOS cases were actually aggressive high-grade lymphomas. The more rapid temporal increases in NOS compared with total NHL reduces concern that improving specificity of classification contributed to the increases observed in many of the NHL subtypes.

Reasons for the increasing incidence of most NHL subtypes are obscure, since well-established major risk factors (e.g., immunosuppression, autoimmunity, and HIV infection) explain, at most, a small fraction of the cases (49,118). The increase is larger than could be explained on the basis of changing diagnostic practices or misclassification (119). Only diffuse small NHL declined, probably because of changing diagnostic practice (120). The meteoric rise in high-grade AIDS-related lymphomas in the 1980s constitutes only 7%–13% of all NHL in the total geographic regions covered by SEER registries (46,49). The rapid increase in follicular NHL among black males remains puzzling.

New Approaches to the Classification of the NHLs

In 1994, the International Lymphoma Study Group proposed a revised European-American lymphoma (REAL) classification (121), with defined subgroups confirmed to have prognostic significance (122). Newly proposed revisions of the World Health Organization (WHO) classification of lymphomas rely heavily on the REAL classification (123), and the new ICD-O-3 field trial version (124) incorporates the WHO classification. Our analysis included cases diagnosed from 1978 through 1995, and the data have not been recoded to the new system. Immunophenotype is an indispensable element of this classification, but we found specification of T- versus B-cell lacking for more than half of NHL cases diagnosed during the 1990s. A recent review of the epidemiology of the REAL classification subtypes of NHL (125) illustrates the potential usefulness of this nomenclature as an aid to descriptive epidemiology.

Conclusion

Our data suggest that evaluation of epidemiologic patterns of NHL according to histologic subtype remains highly informative. While analytic studies have not consistently shown clear variation in NHL risk factors by subtype, the small number of such investigations does not permit firm conclusions. Future epidemiologic studies of NHL should evaluate risk factors according to the six major categories in this study as well as the WHO classification, since we find major incidence variation by age, sex, race, geographic area, and time period.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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