Epidemiology and Prognosis of T-Cell Lymphoma

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Introduction

NHL incidence rates rose steadily in the second half of the twentieth century. This observation motivated the conduct of numerous large-scale population-based epidemiologic studies of NHL in the last decade whose goals were to understand the rising rates and to uncover the etiology of NHL and its heterogeneous subtypes. In these studies, however, T-cell lymphomas and its subtypes are underrepresented due to the low incidence of disease and the relatively small proportion of NHL cases that are considered T-cell lymphomas. Like B-cell lymphomas, T-cell lymphomas comprise multiple subtypes with different incidence rates and patterns that likely reflect their distinct etiologies (e.g., mycosis fungoides and adult T-cell leukemia/lymphoma (ATL)). In recent years, the incidence rates of many B-cell lymphomas have begun to decline in the United States (US). In contrast, incidence rates for T-cell lymphomas have continued to rise. With consortial efforts and multidisciplinary

approaches to epidemiologic research, the major hurdles for uncovering T-cell lymphoma risk factors may finally be surmountable.

Patterns of Occurrence

T/NK-cell lymphoid neoplasms account for approximately 6% of all lymphoid neoplasms. B-cell lymphoid neoplasms account for 80% of all lymphoid neoplasms and Hodgkin lymphomas account for 7%. During the 10-year period from 1997 to 2006 as recorded in the US Surveillance, Epidemiology and End Results (SEER) cancer registries, incidence rates for B-cell lymphoid neoplasms (27.96 per 100,000 persons) was greatly elevated above T/NK-cell lymphoid neoplasms (2.09) and Hodgkin lymphoma (2.71) (Table 2.1). Within T/NK-cell lymphoid neoplasms, incidence rates were highest for peripheral T-cell lymphoma (PTCL) (0.78) followed by mycosis fungoides/Sezary syndrome (0.54) and T/NK-cell lymphoid neoplasms, not otherwise specified (NOS) (0.49). Incidence of ATL was rare in the US (0.04). The most common PTCL subtype was PTCL-NOS (0.41) followed by anaplastic large cell lymphoma (ALCL) (0.28), cutaneous T-cell lymphoma (0.25), and angioimmunoblastic lymphoma (0.10). The remaining PTCL subtypes (subcutaneous panniculitis-like T-cell lymphoma, hepatosplenic T-cell lymphoma, enteropathy type T-cell lymphoma) were rare and had incidence rates of 0.01 per 100,000 persons.

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Table 2.1 Incidence of hematopoietic neoplasms by subtype and ICD-O-3 codes, 13 SEER registries, 1997–2006

Hematopoietic neoplasm subtype	ICD-O-3 codes[a, b]	No.	Rate[c]
Lymphoid neoplasms, total	–	127,234	34.55
B-cell lymphoid neoplasms, total	9590–9591(B), 9596(B), 9670–9671, 9673, 9675(B), 9678–9680, 9684, 9687, 9689–9691, 9695, 9698–9699, 9727(B), 9728, 9731–9734, 9761, 9764, 9820(B), 9823, 9826, 9832(B), 9833, 9835(B), 9836, 9940, 9970(B)	102,100	27.96
T/NK-cell lymphoid neoplasms, total	9590–9591(T/NK), 9596(T/NK), 9675(T/NK), 9700–9702, 9705, 9708–9709, 9714, 9716–9719, 9727(T/NK), 9729, 9820(T/NK), 9827, 9831, 9832(T/NK), 9834, 9835(T/NK), 9837, 9948, 9970(T/NK)	7,868	2.09
Mycosis fungoides/Sézary syndrome	9700–9701	2,037	0.54
Peripheral T-cell lymphoma	9675(T/NK), 9702, 9705, 9708, 9714, 9716, 9827	2,921	0.78
Angioimmunoblastic lymphoma	9705	368	0.10
Anaplastic large cell lymphoma	9714	1,051	0.28
Peripheral T-cell lymphoma, NOS	9675(T/NK), 9702, 9708, 9716, 9827	1,502	0.41
Adult T-cell leukemia/lymphoma	9827	146	0.04
T/NK-cell lymphoid neoplasms, NOS	9590–9591(T/NK), 9596(T/NK), 9709, 9717–9719, 9820(T/NK), 9831, 9948, 9970 (T/NK)	1,812	0.49
Lymphoblastic leukemia/lymphoma[d]	9727–9729, 9835–9837	6,591	1.67
B-cell lymphoblastic leukemia/ lymphoma	9727(B), 9728, 9835(B), 9836	4,012	1.02
T-cell lymphoblastic leukemia/ lymphoma	9727(T/NK), 9729, 9835(T/NK), 9837	1,001	0.25
Unknown type lymphoblastic leukemia/lymphoma	9727, 9835(unknown)	1,578	0.40
Prolymphocytic leukemia	9832–9834	281	0.08
Hodgkin lymphoma	9650–9655, 9659, 9661–9665, 9667	10,644	2.71
Unknown type lymphoid neoplasms	9590–9591(unknown), 9596(unknown), 9675(unknown), 9820(unknown), 9970(unknown)	4,971	1.36

ICD-O International classification of diseases for oncology; *NK* natural killer cell; NOS not otherwise specified; *SEER* Surveillance, Epidemiology, and End Results

[b]Codes followed by parentheses indicate that immunophenotyping data (B-cell, T/NK-cell, or unknown) were used to assign cases to that lymphoid neoplasm subtype
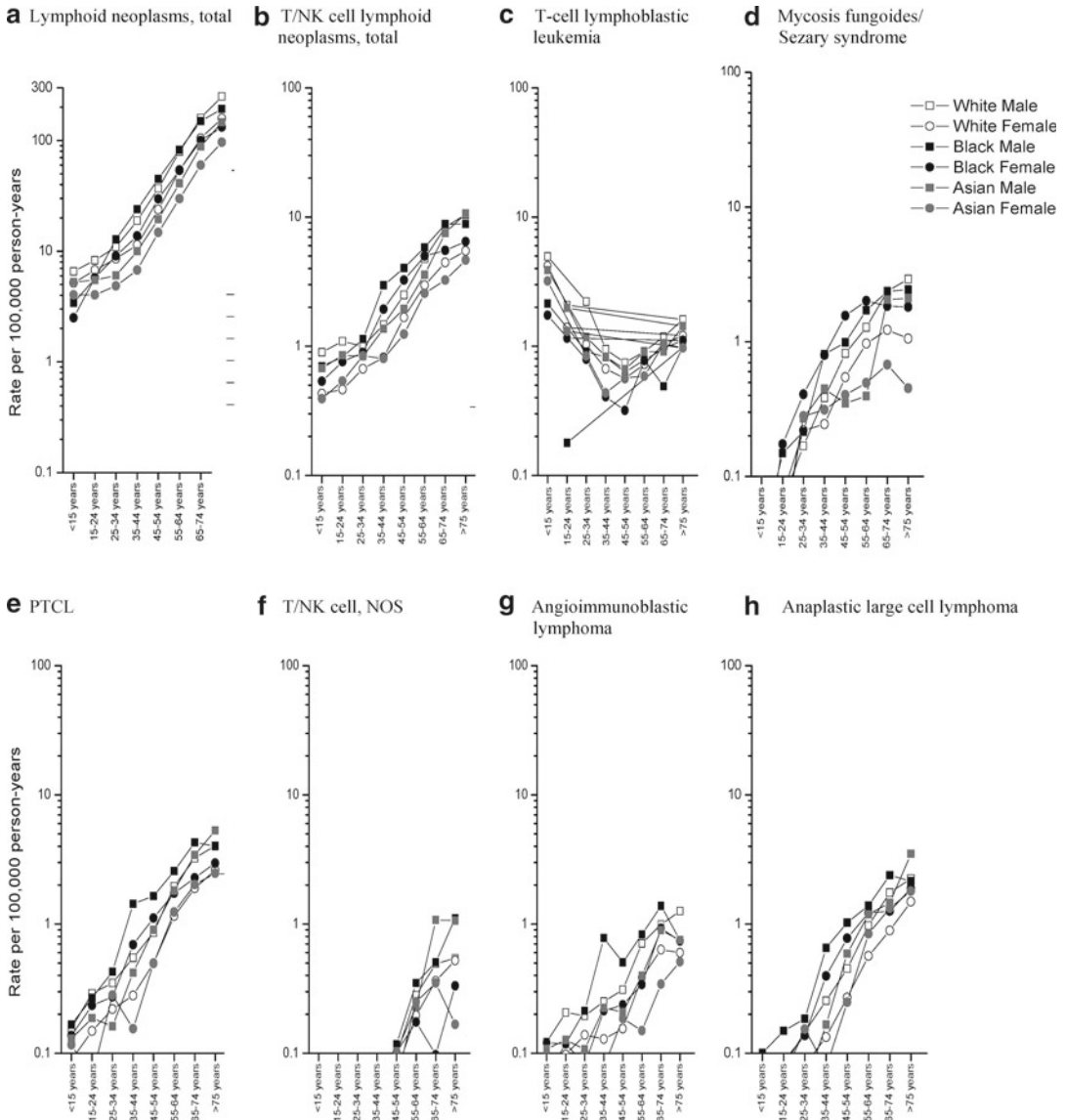
[c]All incidence rates are age-adjusted to the 2000 US population and expressed per 100,000 person-years

[d]Also known as acute lymphoblastic leukemia (ALL)

In general, lymphoid neoplasm incidence increases monotonically with age and is higher in males than females. This pattern is similarly reflected in total T/NK cell lymphoid neoplasms (Fig. 2.1). However, differences emerge between individual subtypes. For example, T-cell lymphoblastic leukemia has a bimodal distribution where children (<15 years) and older adults (≥65 years) have higher incidence. Mycosis fungoides/Sezary syndrome incidence begins in teenagers and T/NK cell-NOS incidence is limited to adults 45 years and above. PTCL incidence rates are higher among Black males and females and angioimmunoblastic lymphoma incidence rates are highest in Black males.

Further differences in risk patterns emerge by demographic groups. Like B-cell lymphoid neoplasms, incidence of T/NK-cell lymphoid neoplasms in all categories of race are higher in men than women (Tables 2.2 and 2.3). However, unlike B-cell lymphoid neoplasms which predominantly develop in white populations, T-cell

Fig. 2.1 Incidence of lymphoid neoplasms by subtype, race, sex, and age, 13 SEER registries, 1997–2006. *All incidence rates are age-adjusted to the 2000 United States population within age groups

lymphoid neoplasms appear to occur similarly in black and white populations. For the 1997–2006 time period within the US SEER cancer registry, incidence rates of T-cell lymphoid neoplasms among black men were 3.06 per 100,000, followed by white men (2.65), and Asian men (2.31) (Table 2.2). Among women, incidence rates were highest among black women (2.28) followed by white (1.49), and Asian women (1.29). This pattern is generally consistent across the T/NK-cell

lymphoid neoplasm subtypes except the PTCL subtype angioimmunoblastic lymphoma where rates are higher among Asian males (0.17) than black (0.15) or white (0.11) males (Tables 2.2 and 2.3).

Incidence rates of all lymphoid neoplasms appear to have plateaued in the US (Fig. 2.2). However, while the incidence of B-cell lymphoid neoplasms has slowed particularly among white men, rates for T/NK-cell lymphoid neoplasms

Table 2.2 Incidence of lymphoid neoplasms by subtype, race, and sex, 13 SEER registries, 1997–2006

Lymphoid neoplasm subtype	Male								Female							
	White		Black		Asian		AI/AN		White		Black		Asian		AI/AN	
	No.	Rate[a]	No.	Rate[a]	No.	Rate[a]	No.	Rate[a]	No.	Rate[a]	No.	Rate[a]	No.	Rate[a]	No.	Rate[a]
Lymphoid neoplasms, total	58,204	44.64	6,072	41.96	4,449	25.16	354	18.77	47,150	29.42	5,352	28.10	3,812	17.55	333	15.93
B-cell lymphoid neoplasms, total	46,885	36.46	4,642	33.89	3,514	20.27	261	14.57	38,213	23.70	4,079	22.19	3,092	14.36	286	13.89
T/NK-cell lymphoid neoplasms, total	3,597	2.65	505	3.06	429	2.31	45	2.10	2,334	1.49	467	2.28	290	1.29	16	0.72
Mycosis fungoides/Sézary syndrome	872	0.65	120	0.77	85	0.46	8	0.45	601	0.39	170	0.83	66	0.28	2	0.07
Peripheral T-cell lymphoma	1,286	0.96	215	1.33	173	0.97	17	0.83	900	0.57	168	0.84	123	0.56	8	0.40
Angioimmunoblastic lymphoma	146	0.11	19	0.15	29	0.17	0	0.00	139	0.09	16	0.08	15	0.07	0	0.00
Anaplastic large cell lymphoma	506	0.37	81	0.46	50	0.26	10	0.49	310	0.20	52	0.26	31	0.14	4	0.17
Peripheral T-cell lymphoma, NOS	634	0.48	115	0.72	94	0.54	7	0.33	451	0.28	100	0.51	77	0.35	4	0.23
Adult T-cell leukemia/lymphoma	36	0.03	18	0.11	12	0.07	2	0.10	39	0.02	26	0.13	10	0.05	0	0.00
T/NK-cell lymphoid neoplasms, NOS	867	0.65	88	0.59	101	0.56	12	0.60	567	0.36	74	0.38	63	0.28	4	0.20
Lymphoblastic leukemia/lymphoma	3,071	2.08	242	1.02	346	1.63	43	1.22	2,327	1.58	217	0.92	274	1.27	35	1.12
B-cell lymphoblastic leukemia/lymphoma	1,828	1.23	123	0.52	206	0.97	24	0.67	1,490	1.01	105	0.45	191	0.89	25	0.76
T-cell lymphoblastic leukemia/lymphoma	527	0.35	71	0.30	68	0.31	7	0.18	236	0.16	52	0.22	35	0.15	2	0.05
Unknown type lymphoblastic leukemia/lymphoma	716	0.49	48	0.21	72	0.35	12	0.37	601	0.40	60	0.25	48	0.23	8	0.31
Prolymphocytic leukemia	148	0.12	20	0.13	6	0.03	1	0.04	88	0.05	10	0.05	5	0.02	0	0.00
Hodgkin lymphoma	4,818	3.29	586	2.95	293	1.38	20	0.85	4,035	2.68	527	2.24	254	1.07	15	0.57
Unknown type lymphoid neoplasms	2,148	1.71	287	1.82	140	0.85	16	0.89	1,942	1.14	216	1.12	128	0.60	8	0.44

AI/AN American Indian or Alaska Native; *CLL/SLL* Chronic lymphocytic leukemia/small lymphocytic lymphoma; *DLBCL* diffuse large B-cell lymphoma; *NK* natural killer cell; *NOS* not otherwise specified; *SEER* surveillance, epidemiology, and end results

[a]All incidence rates are age-adjusted to the 2000 US population and expressed per 100,000 person-years

Surveillance, epidemiology, and end results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 13 Regs Limited-Use, Nov 2008 Sub (1992–2006) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total US, 1969–2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission

Table 2.3 Incidence rate[a] ratios for lymphoid neoplasms by subtype, race, and sex, 13 SEER registries, 1997–2006

Lymphoid neoplasm subtype	Male:Female IRR			White:Black IRR		White:Asian IRR	
	White	Black	Asian	Males	Females	Males	Females
Lymphoid neoplasms, total	1.5	1.5	1.4	1.1	1.0	1.8	1.7
B-cell lymphoid neoplasms, total	1.5	1.5	1.4	1.1	1.1	1.8	1.6
T/NK-cell lymphoid neoplasms, total	1.8	1.3	1.8	0.9	0.7	1.1	1.2
Mycosis fungoides/Sézary syndrome	1.7	0.9	1.6	0.8	0.5	1.4	1.4
Peripheral T-cell lymphoma	1.7	1.6	1.7	0.7	0.7	1.0	1.0
Angioimmunoblastic lymphoma	1.3	1.9	2.6	0.7	1.1	0.6	1.3
Anaplastic large cell lymphoma	1.8	1.8	1.9	0.8	0.8	1.4	1.4
Peripheral T-cell lymphoma, NOS	1.7	1.4	1.5	0.7	0.6	0.9	0.8
Adult T-cell leukemia/lymphoma	1.2	0.8	1.5	0.3	0.2	0.4	0.5
T/NK-cell lymphoid neoplasms, NOS	1.8	1.6	2.0	1.1	1.0	1.2	1.3
Lymphoblastic leukemia/lymphoma	1.3	1.1	1.3	2.0	1.7	1.3	1.2
B-cell lymphoblastic leukemia/lymphoma	1.2	1.2	1.1	2.4	2.3	1.3	1.1
T-cell lymphoblastic leukemia/lymphoma	2.2	1.3	2.0	1.2	0.7	1.1	1.0
Unknown type lymphoblastic leukemia/lymphoma	1.2	0.8	1.5	2.4	1.6	1.4	1.8
Prolymphocytic leukemia	2.3	2.3	1.5	0.9	0.9	3.6	2.3
Hodgkin lymphoma	1.2	1.3	1.3	1.1	1.2	2.4	2.5
Unknown type lymphoid neoplasms	1.5	1.6	1.4	0.9	1.0	2.0	1.9

CLL/SLL Chronic lymphocytic leukemia/small lymphocytic lymphoma; *DLBCL* diffuse large B-cell lymphoma; *IRR* Incidence rate ratio; *NK* natural killer cell; *NOS* not otherwise specified; *SEER* surveillance, epidemiology, and end results

~=Calculation of the IRR was precluded by zero cases diagnosed among Asian males

Bolded IRRs were not statistically significant at $P < 0.05$ (95% CI included 1.0)

95% CIs available from the author

[a]All incidence rates are age-adjusted to the 2000 US population

Surveillance, epidemiology, and end results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 13 Regs Limited-Use, Nov 2008 Sub (1992–2006) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total US, 1969–2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission

continue to rise for men and women of all race groups. Specifically, from 1997 to 2006, incidence rates of T/NK-cell lymphoid neoplasms in the US have risen with an annual percent change of 1.17 (Table 2.4). The annual increase in incidence was highest for Black males (2.2) and Asian females (2.3). Only among Asian males did rates appear to decline during this time period (−0.45). By subtype, rates declined for mycosis fungoides/Sezary syndrome within all race groups (Fig. 2.2 and Table 2.4). Incidence rates for PTCL increased (3.78) and strikingly so for the PTCL subtype, angioimmunoblastic lymphoma (14). Incidence also increased strikingly for PTCL-NOS (5.5) but declined for ALCL (−2.0) (Table 2.4 and Fig. 2.2). That anaplastic large cell lymphoma declined during the same period that angioimmunoblastic lymphomas

increased raises some question regarding potential coding changes within the cancer registry for these two subtypes.

Incidence rates for lymphoid neoplasms also vary by geography and there are some particular differences by subtypes. For example, the human T-cell lymphotropic virus I (HTLV-1) is endemic to Japan and the Caribbean, resulting in elevated rates of ATLs in these regions. In general, the occurrence of lymphoid neoplasms is higher in developed countries. In these countries which are largely of Caucasian descent such as the US, T/NK-cell lymphoid neoplasms comprise less than 10% of all lymphoid neoplasms. There is some evidence, however, that the proportion of T-cell lymphoid neoplasms in Asian countries is higher (15–25%, excluding ATL) [1–3] and that rates of nasal type NK/T-cell lymphoma in
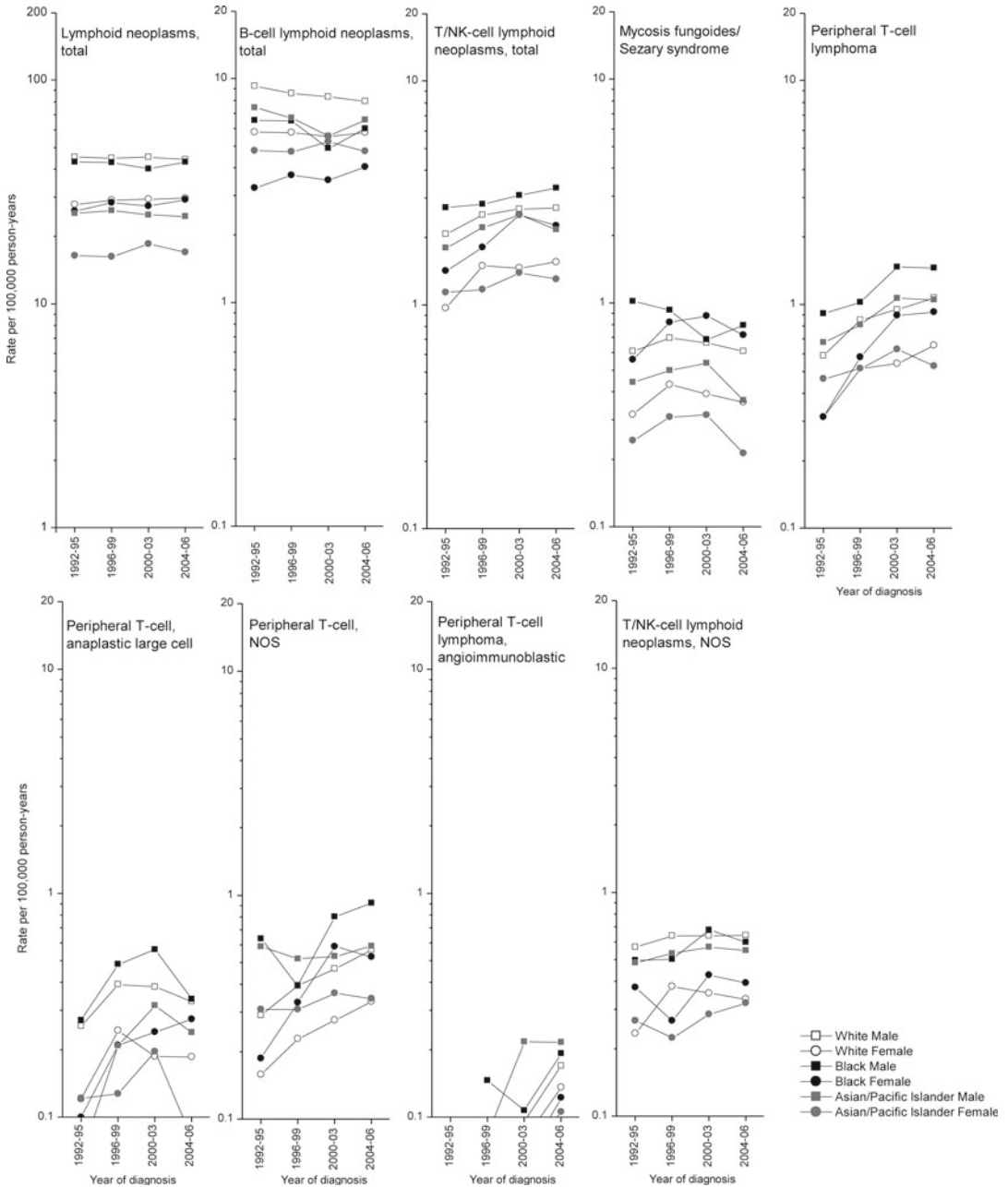
Fig. 2.2 Trends in incidence of lymphoid neoplasms by subtype, race, and sex, 13 SEER registries, 1992–1995 to 2004–2006. *All incidence rates are age-adjusted to the 2000 United States population and presented for four fixed time periods (1992–1995, 1996–1999, 2000–2003, 2004–2006). ^Presentation of trends for certain populations was precluded by at least one annual rate of zero

particular are higher in Asians than Caucasians [4]. Within the US, Asians also have varying rates; among US Asians in four SEER registries (1996–2004), incidence rates are highest among Filipino (1.1), Asian Indian/Pakistani (0.8), and Japanese (0.8) populations; rates are lower than Whites in Korean (0.6), Vietnamese (0.6), and Chinese (0.4) populations [5].

Table 2.4 Annual percent changes in lymphoid neoplasm incidence rates* by subtype, race, and sex, 13 SEER registries, 1997–2006

	Males				Females		
	Total[†]	White	Black	Asian	White	Black	Asian
Lymphoid neoplasms, total	−0.0427	−0.0962	0.0928	−0.7623	0.2345	0.3877	−0.0268
B-cell lymphoid neoplasms, total	0.4161	0.3813	0.3388	−0.4618	0.8241*	0.5558	−0.2574
T/NK-cell lymphoid neoplasms, total	1.1691	0.8756	2.2072	−0.4532	1.3093	0.8126	2.3118
Mycosis fungoides/Sézary syndrome	−1.9107*	−2.0273	−2.6149	−3.0275	−1.5175	−3.0766	−3.0828
Peripheral T-cell lymphoma	3.7821*	3.1657*	4.8475	3.7147	4.5589*	2.4256	−0.0645
Peripheral T—angioimmunoblastic	14.1737*	13.2487*	~	~	16.0677*	14.9347	~
Peripheral T—anaplastic large cell	−2.0075	−2.3261	−3.6173	3.5916	−1.7437	−1.1701	~
Peripheral T—NOS*	5.5460*	5.4049*	9.7284	2.0159	6.0618*	3.575	0.0936
T/NK-cell lymphoid neoplasms, NOS	−0.2212	−0.1506	2.0884	−2.0632	−1.8366	4.9163	5.956
Lymphoblastic leukemia/lymphoma	1.034	1.6265	−0.4829	−0.2968	0.1719	3.6541	3.6677
Prolymphocytic leukemia	−1.9903	−2.6652	7.7941	~	−0.0031	~	~
Hodgkin lymphoma	0.3216	−0.0205	1.899	2.9156	0.0263	2.2964	5.9063*
Unknown type lymphoid neoplasms	−8.4295*	−8.5848*	−9.4694*	−9.6691*s	−8.0173*	−6.2642	−6.6906*

CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma; *DLBCL* diffuse large B-cell lymphoma; *NK* natural killer cell; *NOS* not otherwise specified; *SEER* Surveillance, Epidemiology, and End Results

~=Calculation of the annual percent change was precluded by at least one annual rate of zero

Surveillance, epidemiology, and end results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 13 Regs Limited-Use, Nov 2008 Sub (1992–2006) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total US, 1969–2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission

Risk Factors for T-Cell Lymphomas

Few risk factors for T-cell lymphomas are known. Although numerous studies of NHL were conducted worldwide in the last decade, the low incidence of T-cell lymphomas and the low proportion of NHLs that T-cell lymphomas comprise provided individual studies with few cases and virtually no statistical power to evaluate modest risk factors for T-cell lymphomas or its subtypes. The formation of consortia in the last decade for epidemiologic studies where case-control and/or cohort studies conduct pooled analyses to increase sample sizes to evaluate modest risk factors for tumors and their major subtypes has contributed to the understanding of NHL etiology. Specifically, the International Epidemiology Lymphoma Consortium (InterLymph) has allowed evaluation of over 10,000 NHL cases and a comparable number of controls. The numbers of T-cell lymphomas within the InterLymph Consortium now approaches a thousand. To date, a number of risk factors have been linked to NHL and some of the major NHL subtypes, including: family history of hematopoietic malignancies, medical conditions and viral infections, occupational and environmental exposures, behavioral factors such as dietary intake, and personal exposures such as use of hair dyes. These risk factors and others are summarized with regard to their potential relevance for T-cell lymphomas (Table 2.5).

Family and Personal History

A number of studies including registry databases from Sweden and Denmark [6, 7] have linked increased NHL risk among those with a first-degree relative with NHL. No individual study has had sufficient power to evaluate T-cell lymphoma risk with family history. A recent pooled analysis from the InterLymph Consortium of 10,211 NHL cases and 11,905 controls included 447 T-cell lymphoma cases. In addition to confirming a 50% increase in risk for NHL with family history of NHL, the pooled analysis

Table 2.5 Summary status of potential risk factors for T-cell lymphomas

Risk factors	Status	Risk association	Subtype specificity
Family and personal history			
Family history	Hypothesized	Increased risk	
Personal history	Hypothesized	Increased risk for NHL (numbers too small to delineate T-cell lymphomas)	
Autoimmune disorders			
Celiac disease	Established	Increased risk	Extranodal
Psoriasis	Hypothesized	Increased risk	
Immunosuppressive therapies and organ transplants	Established	Increased risk for all NHL (including T-cell lymphomas)	
Atopy			
Eczema	Hypothesized	Increased risk	
Infections			
HTLV-1	Established	Increased risk	ATLL
HIV, HCV, *Helicobacter pylori*	Hypothesized	Increased risk for NHL (numbers too small to delineate T-cell lymphomas)	
Occupational/pesticide exposures	Hypothesized	Increased risk for NHL (numbers too small to delineate T-cell lymphomas)	
Behavioral risk factors			
Smoking	Hypothesized	No association	Mycosis fungoides, PTCL
Alcohol	Hypothesized	Decreased risk	
Height/weight	Hypothesized	Increased risk for NHL (numbers too small to delineate T-cell lymphomas)	
Sun exposure	Hypothesized	Decreased risk for NHL (numbers too small to delineate T-cell lymphomas)	
Diet/hair dye use	Hypothesized	Increased risk for NHL (numbers too small to delineate T-cell lymphomas)	
Genetic susceptibility			
TNF G-308A	Hypothesized	Increased risk	Mycosis fungoides

reported increased T-cell lymphoma risks among those reporting a first-degree male relative with multiple myeloma (OR = 5.8, 95% CI = 1.5–21.4). T-cell lymphoma risk was also elevated among individuals 50 years or younger and who reported a family history of leukemia (OR = 2.3, 95% CI = 1.0–5.6), compared with individuals who were older than 50 years [8]. There was no elevation in T-cell lymphoma risk among those reporting a family history of NHL or Hodgkin lymphoma.

Based on a US childhood cancer survivor study, children with mycosis fungoides and Sezary syndrome have elevated NHL risks [9]. Risks for lymphoma (NHL standard incidence ratio = 5.08, 95% CI = 3.34–7.38) were also found elevated in a study that followed patients with mycosis fungoides and Sezary syndrome [10].

Whether these subsequent risks for NHL were more likely to be T-cell lymphomas is unclear.

Autoimmune Disorders

Autoimmune conditions are an established risk factor for NHL specific conditions implicated in NHL risk include Sjogren's syndrome, systemic lupus erythematosus, and Celiac disease [11]. Of these, it is well established that Celiac disease patients possess elevated NHL risk that is predominant for T-cell lymphomas. High risk for NHL mortality and risk has been reported in an Italian [12], US [13] and Swedish cohort studies [14], and in a Swedish registry-based study [15]. Results from the pooled InterLymph Consortium analysis of autoimmune conditions and NHL

which included 766 T-cell lymphomas risk further support an association between Celiac disease and extranodal T-cell lymphoma (OR = 6.21, 95% CI = 2.82–13.6) [16]. The study also implicates psoriasis with increased T-cell lymphoma risk (OR = 1.63, 95% CI = 1.03–2.57).

Primary Immunodeficiencies and Organ Transplants

Individuals who are recipients of organ transplants and immunosuppressive therapy also have elevated NHL risks. Although B-cell lymphomas are more common, T-cell lymphomas also develop post-transplantation.

Atopy

Atopic conditions such as asthma, allergies and eczema are hypothesized to induce mild immune deficiencies that would prefer a Th2 immune response and result in decreased NHL risk. Contrary to this hypothesis, a recent pooled analysis of various atopic conditions within the InterLymph Consortium did not report an association with asthma and allergy but did observe increased risk for T-cell lymphoma among those who reported having eczema (OR = 1.92, 95% CI = 1.43–2.58). Further data from cohort studies are needed to confirm these associations in analyses not potentially biased by disease status [17].

Infections

A number of infectious agents are linked to NHL etiology, either by directly causing lymphomagenesis or providing a cellular milieu that depresses immune function or induces chronic inflammation. The association between HTLV-1 and ATL is well established and HTLV-1 was the first retrovirus established as causal for lymphoma [18, 19]. In southern Japan and the Caribbean, HTLV-1 infection is endemic and is attributable to 56 and 78% of ATL cases,

respectively [19]. Further increased ATL risks are reported among those infected with both HTLV-1 and the gastrointestinal parasite also endemic in the same regions, Strongyloides stercoralis [20]. Other infections associated with NHL include the human immunodeficiency virus, hepatitis C virus, and *Helicobacter pylori*, but none affect T-cell lymphomas preferentially.

Occupational Exposures

Occupations linked with elevated NHL risks include: farmers, livestock workers, printers, teachers, wood workers, dry cleaners, barbers, and hairdressers [21, 22]. NHL is one of the malignancies caused by exposure to non-arsenical insecticides; tetrachloroethylene and trichloroethylene; benzene, 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin; and 1,3-Butadiene [23]. Persistent organochlorine exposure including polychlorinated biphenyls, dioxins, furans [24], and pesticide exposure such as DDE [25] and alpha-chlordane [26] have also been associated with increased NHL risk. At present, no preferential risk for T-cell lymphomas has been reported.

Behavioral Risk Factors

Unlike most other cancers, smoking does not appear to be a strong risk factor for developing NHL. By subtypes, however, a pooled analysis from nine case-control studies within the InterLymph Consortium of 6,594 cases reported elevated risks for follicular lymphoma among smokers but not other subtypes [27]. Null associations were reported for T-cell lymphoma and its subtypes, mycosis fungoides, and PTCL. Similar results were reported in a pooled analysis of six European case-control studies of 1,742 cases [28].

Reduced NHL risks have been reported with alcohol consumption. A large pooled analysis of nine case-control studies reported risks of 0.73 for current drinkers [29] and are also supported by cohort studies [30–32]. No differential effect of the association was observed by subtype;

among T-cell lymphomas, decreased risks were observed for mycosis fungoides and PTCL.

Taller individuals and excess weight are also implicated in NHL risk though no preference for T-cell lymphomas has been demonstrated [33]. No preference for T-cell lymphomas has also been demonstrated for sunlight exposure, which is implicated in reducing NHL risk [34]. Other hypothesized NHL risk factors include dietary intake and hair dye use, but to date no associations with T-cell lymphomas have been shown [35].

Genetic Susceptibility

The most consistently demonstrated genetic variants associated with NHL risk are a polymorphism in the promoter region of the tumor necrosis factor (*TNF*) gene (−308G->A) and the interleukin 10 −3575T->A polymorphism, both of which are preferentially associated with DLBCL [36]. Analyses of all NHL subtypes within the InterLymph Consortium for these genetic variants comprising approximately 6,500 NHL cases and 6,700 controls and included over 300 T-cell lymphomas found no association with either proinflammatory cytokine with overall T-cell lymphoma risk. However, increased risk for mycosis fungoides was reported with the *TNF* G-308A variant allele (OR for AG/AA compared to GG genotype=1.53, 95% CI=1.02, 2.28; p-trend=0.03 for each additional variant allele), albeit with just over 100 cases [37]. No other genetic variants have been implicated specifically for T-cell lymphoma risk or that of its subtypes.

Future Directions in Epidemiologic Research

The majority of T-cell lymphomas remain unexplained. As our understanding of NHL epidemiology has moved from studying NHL as a single entity to evaluating individual NHL subtypes with the recognition that the descriptive epidemiology of NHL subtypes are distinct, a similar approach for understanding T-cell lymphomas is clearly needed. To date, most epidemiologic studies have combined the heterogeneous T-cell

lymphoma subtypes into a single entity to increase sample size and power for association studies. However, not only do T-cell lymphoma subtypes have differential treatment, survival and prognosis, but their distinct descriptive epidemiology clearly suggest differences in their etiology and thus also require evaluation as individual entities.

Based on descriptive epidemiology, we know that there are striking differences between T-cell lymphoma subtypes, by age, over time and by race/ethnicity. Based on epidemiologic research and consortia-based pooling efforts of NHL to date, potential risk factors for T-cell lymphoma and some subtypes include Celiac disease for extranodal T-cell lymphomas and a genetic variant in *TNF* for mycosis fungoides. Risk factors that are inversely associated with T-cell lymphomas include alcohol consumption and exposure to sunlight. Although a growing number of viral and bacterial infections are associated with NHL, their specific role in T-cell lymphomas remains unclear, with the exception of HTLV-1 and acute T-cell leukemia/lymphoma (ATLL). Translating clues from case reports to epidemiologic associations will also remain an important avenue of research, such as research on the reported links between breast implants and ALCLs of the breast. Research in understanding the role of genetic variants in T-cell lymphoma etiology is still in its infancy as most studies have been underpowered to adequately evaluate genetic associations. We thus encourage the inclusion of T-cell lymphomas from consortial efforts in ongoing genome-wide association studies to further our understanding of genes and pathways that may play important roles in T-cell lymphoma etiology.

Risk factors for T-cell lymphomas identified from case-control studies will require further confirmation from cohort studies where survival bias is minimized. For some exposures, cohort studies will be needed to establish temporality, particularly where prediagnostic specimens are optimal for evaluation. For example, some biomarker-based exposures such as persistent organochlorine exposure that can be measured in serial prediagnostic serum are optimally measured prospectively. Combining data from epidemiologic case-control and cohort studies with large clinical series may also prove fruitful for overcoming

the rarity of the tumor for identifying additional T-cell lymphoma risk factors. In addition, the ability to incorporate detailed clinical data to epidemiologic analyses may further our understanding of T-cell lymphoma etiology. Within clinical case series, case–case comparisons may also be beneficial for identifying similar or distinct etiologies across subtypes. Finally, continued attention to striking individual case reports will be instrumental for generating new hypotheses and providing new clues with regard to the etiology of T-cell lymphomas and their subtypes.

Prognosis of T-Cell Lymphoma

Peripheral T-Cell Lymphoma-Not Otherwise Specified

This is the most common type of peripheral T-cell NHL and is a heterogeneous mix of different types of PTCL. PTCL-NOS is the "diffuse large cell" equivalent of B-cell NHL. There are two morphologic variants recognized, the T-zone lymphoma variant and the lymphoepithelioid cell variant. Patients with PTCL-NOS have predominantly nodal lymphoma that presents in adults (median age 61 years), with a male: female ratio of 1.5:1.0 [38]. Patients typically have advanced stage disease with 60% having stage IV disease and many patients having unfavorable characteristics such as B-symptoms, elevated lactic dehydrogenase (LDH), bulky disease, poor performance status, and extranodal disease so that >50% of patients fall into the unfavorable International Prognostic Index (IPI) category 3–5 [37]. Another prognostic model for PTCL-NOS has been utilized by Gallamini et al. [39] which uses the characteristics of age >60, LDH > normal, performance status ≥ 2, and bone marrow involvement to predict outcome and was found to be more discriminatory that the standard IPI for this group of patients.

Angioimmunoblastic Lymphoma

Angioimmunoblastic T-cell lymphoma (AITL), previously known as angioimmunoblastic lymphadenopathy with dysproteinemia, was the second most common PTCL in the International T-Cell Lymphoma Classification Project [40]. This type accounts for 18.5% of the PTCL's. The median age at diagnosis is 64 years, with a male predominance and the majority of patients present with advanced stage disease. Other features include a high percentage of patients with B-symptoms, skin rash, effusions, hypergammaglobulinemia, and other immunologic or rheumatologic abnormalities [41]. The prognosis of AITL is similar to PTCL-NOS with only about 10% of patients alive 10 years after their diagnosis (Fig. 2.3) [40].

Anaplastic Large Cell Lymphoma (Primary Systemic Type)

ALCL, primary systemic type accounts for 2–3% of all NHLs [1] and 10.2% of all T/NK-cell lymphomas [40]. This NHL is usually nodal, although extranodal sites can certainly be involved as well. There are two major subtypes of systemic ALCL, anaplastic lymphoma kinase (ALK)-positive and ALK-negative. ALK-positive systemic ALCL is typically diagnosed in younger patients (median age 34 years, with a male predominance) and ALK-negative in older ones (median age 58 years), although this is not an exclusive cutoff [40]. The ALK status of patients with systemic ALCL is very important as patients with ALK-positive ALCL have a 5-year OS of 70% compared to a 5-year OS of 49% for ALK-negative ALCL [40]. The chromosomal translocation t(2;5)(p23;q35) is associated with this type of lymphoma and results in the fusion protein NPM–ALK [42] (Fig. 2.3).

ALCL, Primary Cutaneous

This is a rare type of NK/T-cell lymphoma, occurring in 1.7% of the T-cell lymphomas [40]. It typically presents in one or more areas in the skin, often in the same region of the body. It is most frequently ALK-negative, but has in general a fairly good prognosis with 5-year OS of 90% and 5-year progression-free survival of 55% [40]. This pattern indicates an indolent type of lymphoma with relapses and the ability to treat the patient repeatedly with either chemotherapy and/or radiotherapy.
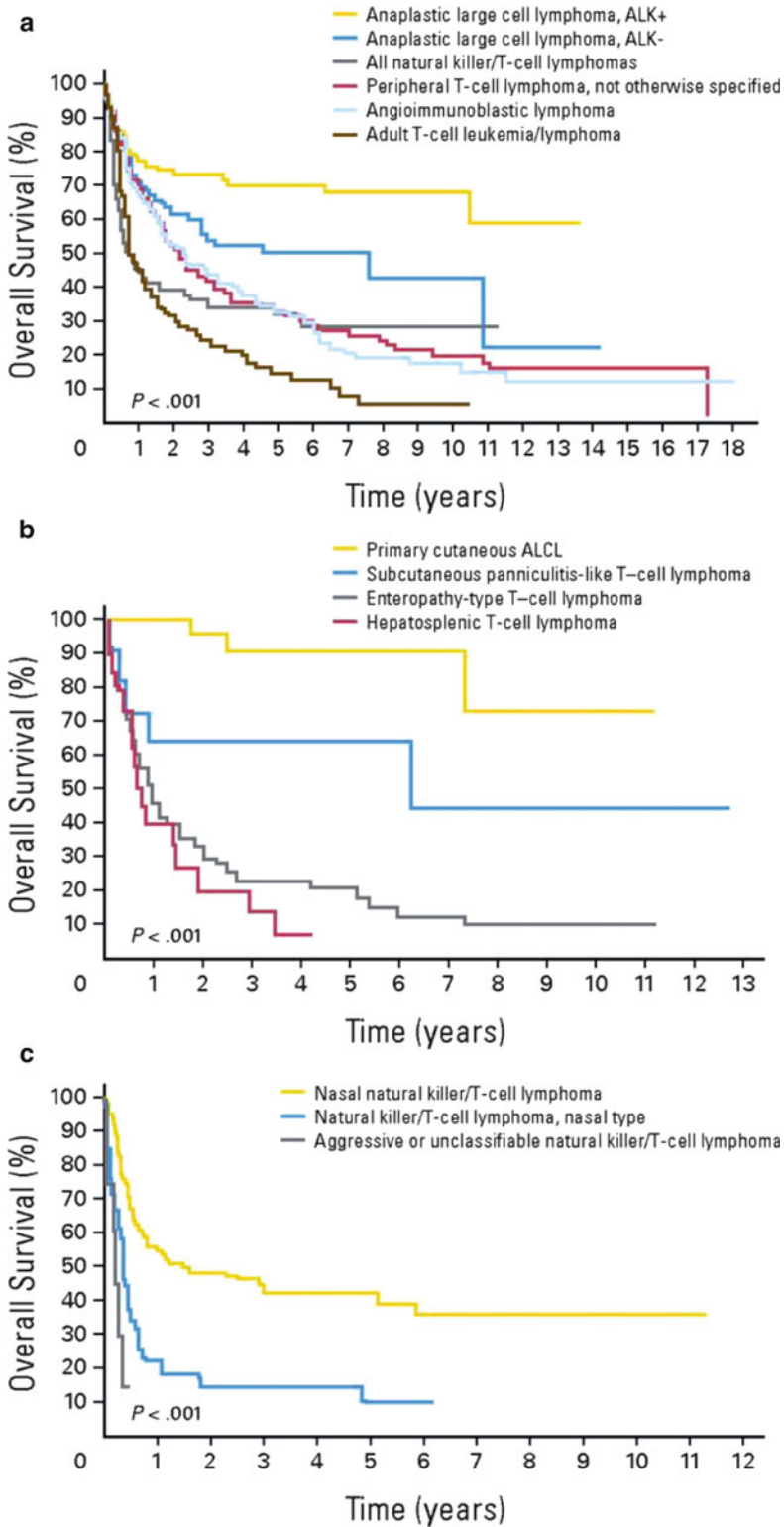
Fig. 2.3 Overall survival of various subtypes of PTCL (Reprinted from Vose et al. [40], With permission from American Society of Clinical Oncology)

Extranodal NK/T-Cell Lymphoma, Nasal and Extranasal (Nasal Type)

These lymphomas were previously called angiocentric lymphomas and are found mostly in Asia, South, and Central America [43]. Nasal NK/T-cell lymphoma is typically seen in the nasal and paranasal sinus areas and is associated with EBV infection [44]. These patients often have localized stage I/II disease but an aggressive clinical course. Patients with extranasal NK/T-cell lymphoma (nasal type) typically present with other extranodal sites of disease (skin, respiratory tract, gastrointestinal, and genitourinary). The 5-year OS with this type of lymphoma is 42% from the International T-cell Study [40] (Fig. 2.3).

Acute T-Cell Leukemia/Lymphoma

ATLL has four subtypes based on clinicopathologic features and prognosis: acute, lymphoma, chronic, and smoldering. Patients with the acute type present with Hypercalcemia, leukemic manifestations, bone and tumor lesions and have a very poor prognosis with a median survival time of 6 months [45]. Patients with the lymphomatous type typically have nodal, hepatosplenic, bone, and gastrointestinal involvement and a median survival of 10 months. Patients with the chronic and smoldering type have a more indolent course. The retrovirus HTLV-1 is critical to the development of ATLL [46]. In endemic areas such as southern Japan, up to 40% of the population is infected with the virus. However, ATLL develops in only 2–3% of the patients who are carriers of the HTLV-1 virus.

Other rare subtypes of PTCL such as hepatosplenic T-cell lymphoma, enteropathy type T-cell lymphoma, and subcutaneous panniculitis type T-cell lymphoma (gamma-delta subtype) have a very poor prognosis with standard therapy.

Summary

Despite the overall decline observed for non-Hodgkin lymphoma incidence, the incidence of T-cell lymphomas continues to rise. The distinct incidence patterns by T-cell lymphoma subtypes suggests that risk factors may also be specific to each T-cell lymphoma subtype as reflected in two of the established risk factors (e.g., celiac disease and extranodal T-cell lymphomas; HTLV-1 and ATLL). This is consistent with the distinct clinical characteristics and prognosis that is observed for each T-cell lymphoma subtype. A predominance of some T-cell lymphoma subtypes by geographic locale (e.g., ATLL and extranodal NK/T-cell lymphoma) further supports the hypothesis of distinct etiologies and need for treatment by subtype. The rarity of T-cell lymphomas has historically posed challenges for furthering our understanding of these tumors. However, we expect important clues to emerge as on-going large international consortium efforts aim to accrue sufficient sample sizes of T-cell lymphomas and its subtypes for both etiological and prognostic studies.

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