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Original Article

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Nationwide Statistical Analysis of Lymphoid Malignancies in Korea

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Purpose

Regional differences in the incidence of lymphoid malignancies have been reported worldwide, but there has been no large-scale epidemiologic analysis in Korea. The aim of this study was to provide a nationwide population-based statistical analysis of Korean patients with lymphoid malignancies.

Materials and Methods

The Korea Central Cancer Registry analyzed the incidence and survival of patients with lymphoid malignancies from the Korean National Cancer Incidence Database. Diseases were grouped by clinically relevant categories based on the 2008 World Health Organization classification.

Results

Overall 65,948 lymphoid diseases were identified between 1999 and 2012. The incidence of most subtypes increased with age, except for precursor cell neoplasms. Male predominance (male:female ratio=1.28:1) was observed. In 2012, annual age-standardized incidence rates per 100,000 persons of Hodgkin's lymphoma, mature B-cell neoplasm, mature T/natural killer (NK)–cell neoplasm, and precursor cell neoplasm were 0.46, 6.60, 0.95, and 1.50, respectively, and they increased yearly from 1999. Composite Hodgkin's and non-Hodgkin's lymphomas were extremely rare. Survival improvement estimated using 5-year relative survival rate was observed in patients with Hodgkin's lymphoma (71.1%-83.0%), diffuse large B-cell lymphoma (49.5%-61.5%), plasma cell neoplasms (20.2%-36.9%), and lymphoblastic lymphoma/leukemia (41.5%-56.3%) between 1993 and 2012. However, survival rates of T/NK-cell lymphoma (excluding cutaneous T-cell lymphoma) ranged from 40.5%-43.5% during the study period. Survival rates decreased with age in most subtypes.

Conclusion

This report presented the subtype-specific statistical analysis of lymphoid malignancies in the Korean population, showing increasing incidences and survival rates in most subtypes.

Key words
Epidemiology, Incidence, Survival, Hematologic neoplasms, Republic of Korea

Introduction

Lymphoid malignancies are a diverse group of neoplasms with different clinical presentations, histology, and biology. They are classified by the morphology, immunophenotype, cytogenetics, and clinical characteristics. The etiology of lymphoid neoplasms is not fully understood. Thus, combining an epidemiologic study with a biological study is helpful for understanding the pathogenesis of each disease.

Different incidences of lymphoid malignancies between regions have been reported [1]. Asian countries have been known to show a relatively lower incidence than the other countries in North America and Europe. In terms of the subtypes of lymphoid malignancies, it also varies in each region. For example, Asian populations show a higher incidence of mature T/natural killer (NK)–cell lymphoma and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (mucosa-associated lymphoid tissue lymphoma), in contrast, Western population show higher incidence of follicular lymphoma and chronic lymphocytic leukemia (CLL) [2,3]. The distribution of lymphoma-associated viruses such as Epstein-Barr virus and human T-lymphoblastic virus-1 has been proposed as a risk factor for the high incidence of specific subtypes of mature T/NK-cell lymphoma in Asian people, but genetic factors may also affect the incidence [4,5].

The classification of hematologic malignancies mainly focused on morphologic and immunophenotypic characteristics before 1990s [6-8], but it has been modified to include cytogenetic characteristics which provide an improved understanding of tumor pathogenesis. The most recent classification of diseases for oncology, International Classification of Diseases for Oncology, third edition (ICD-O-3) was published in 2000 [9] and updated in 2013 to include the changes from the World Health Organization (WHO) classification published in 2008 [2]. Recent cancer registry studies have adopted this ICD-O-3, because it more accurately reflects our recent understanding of these diseases [10,11].

We have published nationwide statistical analyses of hematologic malignancies based on the Korea Central Cancer Registry (KCCR) in 2012 [12]. However, the data was not based on the ICD-O-3 classification. Therefore, to understand the comprehensive incidence and survival of lymphoid malignancies in Korea, we conducted present study with available ICD-O-3 data from the KCCR.

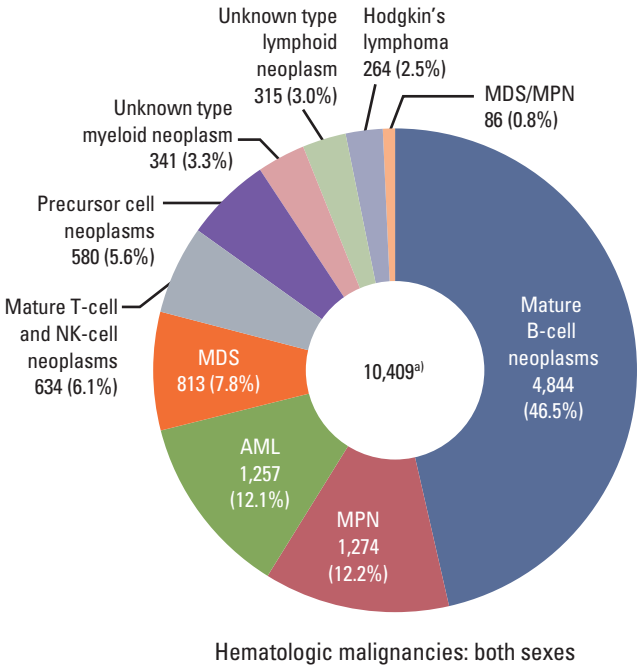
Materials and Methods

The Korean Ministry of Health and Welfare started the KCCR, a nationwide hospital-based cancer registry in 1980. In 1999, the KCCR expanded to include the entire population in the population-based cancer registry program. Incidence data on lymphoid malignancies between 1999 and 2012 was obtained from the Korean National Cancer Incidence Database (KNCIDB).

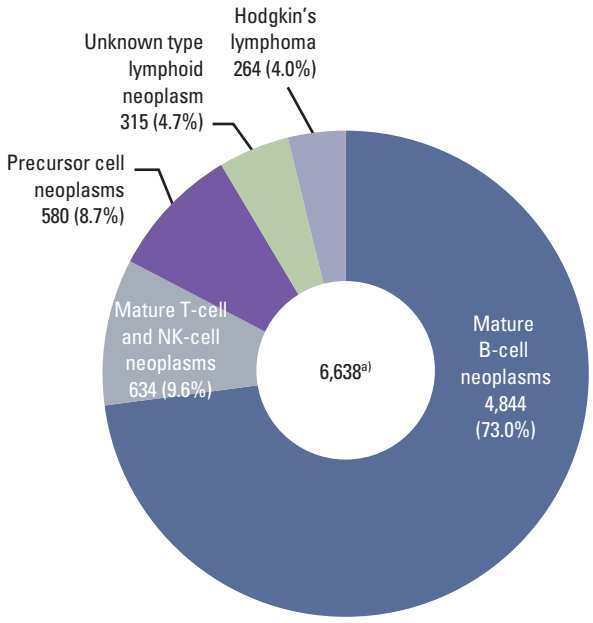
The classification of lymphoid malignancies was categorized to account for incidence and clinical characteristics based on the ICD-O-3 [9]. The codes for lymphoid malignancies were grouped into five clinically relevant categories based on the 2008 WHO classification [2]: Hodgkin's lymphoma (HL), mature B-cell neoplasms, mature T-cell and NK-cell neoplasm, precursor cell neoplasm, and unknown type of lymphoid neoplasm (S1 Table).

The crude incidence rates (CR) and age-specific incidence rates of each subtype of lymphoid malignancy were calculated. The CR per 100,000 persons was calculated as an incidence rate based on the frequency of the disease in the entire population by dividing the total number of events (N) by the total number of person-year of observation (P) and multiplying the result by 100,000. The age-specific incidence rates per 100,000 within an age group (i) were calculated by dividing the number of incident cases observed in the age group (N_i) by the number of corresponding person-year of observation (P_i) and multiplying the result by 100,000. Age-standardized incidence rates (ASRs), a weighted average of crude age-specific rates, were calculated using the Segi's world standard population [13]. Changes in the annual ASRs were examined by calculating the annual percentage change (APC) over a time period as $(\exp(b)-1)\times 100$, where b is the slope of the regression of log(ASR) on a calendar year using the following linear regression equation: $E(\log(ASR) \mid \text{year}) = a + b\ \text{year}$ [14].

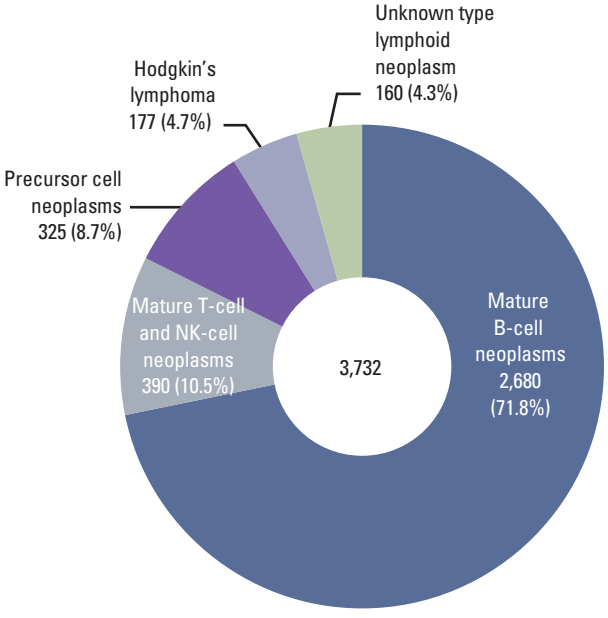
For the survival analyses, cases that were diagnosed as lymphoid malignancies and have available data in the KNCIDB between 1993 and 2012 were included. The patient status was followed until December 31, 2013. The relative survival rate (RSR) was estimated by comparing the observed survival of cancer patients with the expected survival of the general population [15]. Five-year RSR was calculated based on the Ederer II method using the algorithm created by Paul Dickman in SAS [16,17]. All analyses were performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC).



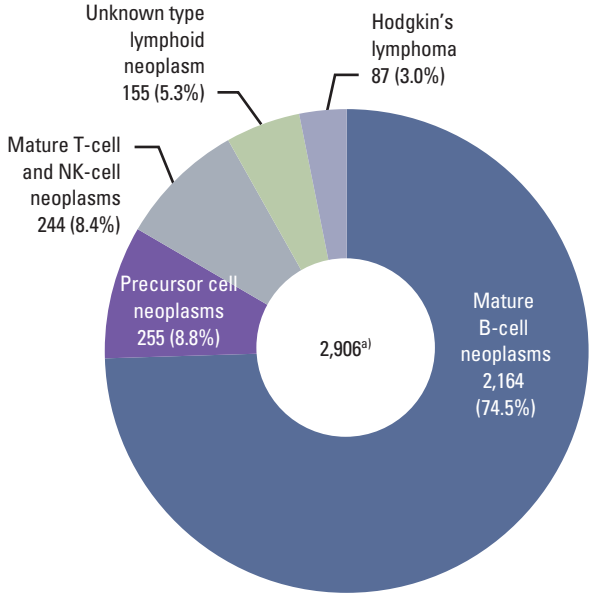
Hematologic malignancies: both sexes



Lymphoid malignancies: both sexes



Lymphoid malignancies: men



Lymphoid malignancies: women

Fig. 1. Incident cases of lymphoid malignancies in Korea, 2012. NK, natural killer; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; MPN, myeloproliferative neoplasm. a)Include one case of composite Hodgkin's and non-Hodgkin's lymphoma.

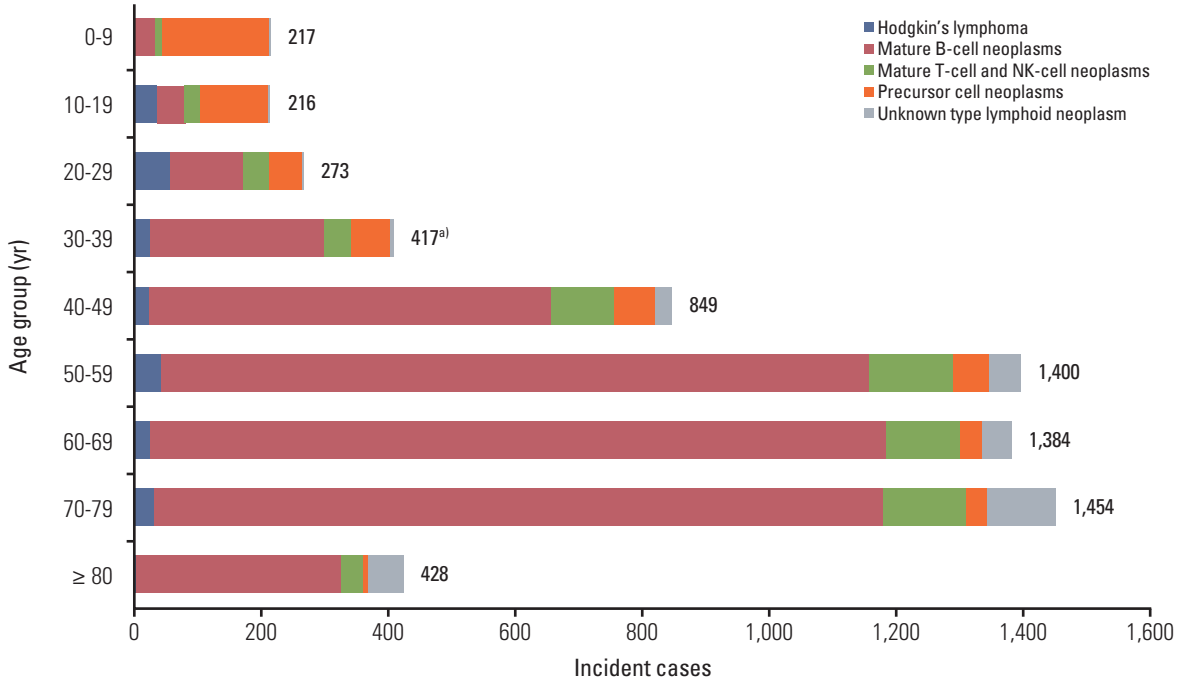


Fig. 2. Incident cases of lymphoid malignancies by age group in Korea, 2012. NK, natural killer. a)All lymphoid malignancies include one case of composite Hodgkin's and non-Hodgkin's lymphoma.

Results

1. Incidences of lymphoid malignancies in 2012

A total of 10,409 cases of hematologic malignancies occurred in 2012, including 6,638 lymphoid malignancies (63.8%) (3,732 men and 2,906 women, male:female ratio=1.28:1) (Fig. 1). This means that the proportions of lymphoid malignancy were 3.3% and 2.6% of all cancers in men and women, respectively. Among all lymphoid malignancies in men, mature B-cell neoplasms (71.8%) were the most frequent, followed by mature T-cell and NK-cell neoplasms (10.5%), and precursor cell neoplasms (8.7%). In women, mature B-cell neoplasms (74.5%) were the most frequent, followed by precursor cell neoplasms (8.8%), and mature T-cell and NK-cell neoplasms (8.4%).

Patients with aged between 70 and 79 years the highest incidence of lymphoid malignancies in 2012, followed by those aged 50 to 59 years, and then 60 to 69 years (Fig. 2). The precursor cell neoplasms were the most prevalent disease type in patients aged group 0-19 years, whereas mature B-cell neoplasms were the most prevalent in those aged more than 20 years.

2. Changes in incidences of lymphoid malignancies between 1999 and 2012

The incident cases of each subtype of lymphoid malignancies and trends in CR and ASR between 1999 and 2012 are shown in Table 1. During the study period, 65,948 lymphoid malignancies were registered. The overall ASR of all lymphoid malignancies increased from 6.9 to 9.9 during the study period. The APC was 3.2% between 1999 and 2012, and it was statistically significant. The ASRs increased from 0.24 to 0.46 in HL (APC, 5.0%; $p < 0.05$), from 3.41 to 6.60 in mature B-cell neoplasm (APC, 5.6%; $p < 0.05$), from 0.47 to 0.95 in mature T-cell and NK-cell neoplasm (APC, 6.6%; $p < 0.05$), and from 1.33 to 1.50 in precursor cell neoplasm (APC, 1.4%; $p < 0.05$). The ASR of cases categorized as "unknown type lymphoid neoplasm" decreased from 1.44 to 0.41 (APC, –9.3%; $p < 0.05$).

3. Estimated RSRs of lymphoid malignancies

The 5-year RSRs of patients with lymphoid malignancies in 5-year intervals (1993-1997, 1998-2002, 2003-2007, and 2008-2012) are shown in Table 2. HL was associated with better survival than the other disease categories. Decreasing survival with age was observed in most disease types of lymphoid malignancies, with poor prognoses in elderly patients. Especially

Table 1. Number of lymphoid malignancies and trend in crude incidence rates and age-standardized incidence rates

Site		Total	Year														APC
			1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Hodgkin's lymphoma	Cases	2,651	119	133	147	143	158	204	157	176	204	217	220	247	262	264	
	CR	0.39	0.25	0.28	0.31	0.30	0.33	0.42	0.32	0.36	0.42	0.44	0.44	0.50	0.52	0.52	
	ASR	0.35	0.24	0.26	0.29	0.28	0.30	0.39	0.29	0.34	0.37	0.40	0.39	0.43	0.48	0.46	5.0[a]
Hodgkin's lymphoma, nodular lymphocyte predominant	Cases	62	< 5	< 5	< 5	< 5	5	< 5	< 5	< 5	< 5	< 5	8	9	6	5	
	CR	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.02	0.02	0.01	0.01	
	ASR	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.01	0.02	0.01	0.01	4.1
Classical Hodgkin's lymphoma	Cases	2,589	115	130	143	140	153	202	154	172	200	215	212	238	256	259	
	CR	0.38	0.24	0.27	0.30	0.29	0.32	0.42	0.32	0.35	0.41	0.44	0.43	0.48	0.51	0.51	
	ASR	0.34	0.23	0.26	0.28	0.28	0.29	0.39	0.29	0.33	0.37	0.40	0.38	0.41	0.47	0.45	5.0[a]
Mature B-cell neoplasms	Cases	42,647	1,650	1,613	1,895	2,044	2,425	2,663	2,877	3,088	3,323	3,575	4,024	4,154	4,472	4,844	
	CR	6.24	3.50	3.39	3.96	4.25	5.02	5.49	5.91	6.32	6.76	7.24	8.10	8.33	8.92	9.62	
	ASR	5.09	3.41	3.26	3.71	3.89	4.46	4.76	4.95	5.16	5.34	5.55	6.01	6.05	6.30	6.60	5.6[a]
Chronic lymphocytic leukemia /Small lymphocytic lymphoma	Cases	1,495	90	65	87	103	81	102	89	126	102	104	126	116	147	157	
	CR	0.22	0.19	0.14	0.18	0.21	0.17	0.21	0.18	0.26	0.21	0.21	0.25	0.23	0.29	0.31	
	ASR	0.18	0.19	0.13	0.17	0.20	0.15	0.18	0.15	0.20	0.16	0.16	0.18	0.16	0.20	0.20	1.0
Immunoproliferative diseases	Cases	310	7	8	20	16	14	15	20	20	27	30	32	27	36	38	
	CR	0.05	0.01	0.02	0.04	0.03	0.03	0.03	0.04	0.04	0.05	0.06	0.06	0.05	0.07	0.08	
	ASR	0.04	0.01	0.02	0.04	0.03	0.03	0.03	0.03	0.03	0.04	0.05	0.05	0.04	0.05	0.05	8.0[a]
Mantle cell lymphoma	Cases	734	27	22	32	22	36	50	48	67	50	68	58	80	70	104	
	CR	0.11	0.06	0.05	0.07	0.05	0.07	0.10	0.10	0.14	0.10	0.14	0.12	0.16	0.14	0.21	
	ASR	0.09	0.06	0.04	0.06	0.04	0.07	0.09	0.08	0.11	0.08	0.10	0.08	0.11	0.09	0.13	7.1[a]
Follicular lymphoma	Cases	1,498	76	57	74	89	92	77	69	102	107	124	128	132	175	196	
	CR	0.22	0.16	0.12	0.15	0.18	0.19	0.16	0.14	0.21	0.22	0.25	0.26	0.26	0.35	0.39	
	ASR	0.18	0.16	0.11	0.14	0.16	0.17	0.13	0.12	0.17	0.18	0.20	0.19	0.19	0.25	0.28	5.1[a]
Diffuse large B-cell lymphoma	Cases	19,659	856	872	988	997	1,154	1,287	1,320	1,395	1,545	1,613	1,758	1,821	2,003	2,050	
	CR	2.88	1.81	1.83	2.06	2.07	2.39	2.65	2.71	2.85	3.14	3.26	3.54	3.65	4.00	4.07	
	ASR	2.34	1.75	1.74	1.92	1.88	2.10	2.29	2.27	2.32	2.47	2.50	2.63	2.65	2.82	2.77	4.0[a]
Burkitt's lymphoma/Leukemia	Cases	976	25	32	30	63	58	75	61	85	92	82	83	92	92	106	
	CR	0.14	0.05	0.07	0.06	0.13	0.12	0.15	0.13	0.17	0.19	0.17	0.17	0.18	0.18	0.21	
	ASR	0.16	0.06	0.09	0.08	0.16	0.14	0.18	0.14	0.19	0.20	0.18	0.20	0.23	0.21	0.25	9.6[a]
Marginal zone lymphoma	Cases	6,716	100	73	96	193	370	379	476	519	507	632	790	790	876	915	
	CR	0.98	0.21	0.15	0.20	0.40	0.77	0.78	0.98	1.06	1.03	1.28	1.59	1.58	1.75	1.82	
	ASR	0.79	0.20	0.14	0.18	0.35	0.66	0.66	0.81	0.86	0.82	0.99	1.19	1.17	1.25	1.28	18.4[a]

Table 1. Continued

Site		Total	Year														APC
			1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
B-Cell prolymphocytic leukemia	Cases	32	0	0	0	0	0	< 5	0	< 5	< 5	< 5	7	8	5	< 5	
	CR	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.02	0.01	0.01	
	ASR	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.00	6.6
Hairy cell leukemia	Cases	58	< 5	< 5	6	< 5	< 5	< 5	< 5	< 5	< 5	6	8	6	6	< 5	
	CR	0.01	0.01	0.00	0.01	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.01	
	ASR	0.01	0.01	0.00	0.01	0.00	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01	0.01	0.00	3.4
Plasma cell neoplasms	Cases	11,169	466	482	562	560	616	673	791	767	889	913	1,034	1,082	1,062	1,272	
	CR	1.63	0.99	1.01	1.17	1.16	1.28	1.39	1.62	1.57	1.81	1.85	2.08	2.17	2.12	2.53	
	ASR	1.30	0.98	0.99	1.12	1.07	1.14	1.19	1.34	1.26	1.39	1.37	1.48	1.48	1.40	1.63	3.7[a)]
Mature T-cell and NK-cell neoplasms	Cases	6,612	232	233	265	300	414	441	515	531	503	591	649	654	650	634	
	CR	0.97	0.49	0.49	0.55	0.62	0.86	0.91	1.06	1.09	1.02	1.20	1.31	1.31	1.30	1.26	
	ASR	0.82	0.47	0.46	0.51	0.58	0.77	0.82	0.91	0.92	0.86	0.97	1.05	0.98	0.99	0.95	6.6[a)]
T lymphoma cutaneous	Cases	744	21	22	18	28	34	36	49	57	49	83	89	87	91	80	
	CR	0.11	0.04	0.05	0.04	0.06	0.07	0.07	0.10	0.12	0.10	0.17	0.18	0.17	0.18	0.16	
	ASR	0.09	0.04	0.04	0.04	0.05	0.06	0.07	0.09	0.11	0.08	0.15	0.15	0.14	0.15	0.13	12.5[a)]
Other T and NK- cell lymphomas	Cases	5,868	211	211	247	272	380	405	466	474	454	508	560	567	559	554	
	CR	0.86	0.45	0.44	0.52	0.57	0.79	0.84	0.96	0.97	0.92	1.03	1.13	1.14	1.12	1.10	
	ASR	0.72	0.42	0.41	0.47	0.53	0.71	0.75	0.81	0.82	0.77	0.83	0.89	0.84	0.84	0.81	5.9[a)]
Precursor cell neoplasms	Cases	7,409	533	479	521	518	520	480	501	526	536	524	569	581	541	580	
	CR	1.08	1.13	1.01	1.09	1.08	1.08	0.99	1.03	1.08	1.09	1.06	1.15	1.16	1.08	1.15	
	ASR	1.35	1.33	1.19	1.31	1.30	1.31	1.22	1.26	1.35	1.37	1.35	1.46	1.50	1.44	1.50	1.4[a)]
Lymphoblastic lymphoma	Cases	749	46	37	52	52	53	58	38	63	45	47	54	66	60	78	
	CR	0.11	0.10	0.08	0.11	0.11	0.11	0.12	0.08	0.13	0.09	0.10	0.11	0.13	0.12	0.15	
	ASR	0.13	0.10	0.09	0.12	0.13	0.12	0.14	0.09	0.15	0.11	0.11	0.14	0.16	0.13	0.18	3.3[a)]
Lymphoblastic leukemia	Cases	6,660	487	442	469	466	467	422	463	463	491	477	515	515	481	502	
	CR	0.97	1.03	0.93	0.98	0.97	0.97	0.87	0.95	0.95	1.00	0.97	1.04	1.03	0.96	1.00	
	ASR	1.22	1.23	1.10	1.19	1.17	1.19	1.09	1.17	1.21	1.25	1.23	1.33	1.34	1.31	1.32	1.2[a)]
Composite Hodgkin's and non-Hodgkin's lymphoma	Cases	11	0	< 5	< 5	0	0	0	0	0	< 5	0	< 5	0	< 5	< 5	
	CR	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.00	0.00	
	ASR	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.5
Unknown type lymphoid neoplasm	Cases	6,618	699	668	661	601	455	494	434	431	478	337	339	320	386	315	
	CR	0.97	1.48	1.41	1.38	1.25	0.94	1.02	0.89	0.88	0.97	0.68	0.68	0.64	0.77	0.63	
	ASR	0.80	1.44	1.34	1.29	1.16	0.84	0.90	0.76	0.73	0.77	0.52	0.50	0.46	0.53	0.41	–9.3[a)]

Table 1. Continued

Site		Total	Year												APC
			1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
All lymphoid malignancies	Cases	65,948	3,233	3,127	3,490	3,606	3,972	4,282	4,484	4,752	5,047	5,244	5,804	5,956	6,313	6,638	
	CR	9.65	6.85	6.58	7.29	7.49	8.22	8.83	9.21	9.72	10.27	10.61	11.69	11.94	12.60	13.18	
	ASR	8.41	6.89	6.51	7.11	7.21	7.68	8.09	8.17	8.50	8.71	8.80	9.42	9.42	9.74	9.93	3.2[a)]

APC, annual percentage change; CR, crude incidence rate; ASR, age-standardized incidence rate; NK, natural killer. [a)]The annual percent change is statistically different from zero ($p < 0.05$).

in patients with precursor cell neoplasms, abrupt decrease in survival rates were observed between pediatric patients (aged 0-14 years), adolescents and young adults (aged 15-34 years), and adults (aged 35 years or more).

4. Changes in the RSRs by major subtypes

The 5-year RSRs of patients with lymphoid malignancies continually increased from 1993 to 2012, from 45.3% to 61.7%, with an increment of 16.4% between these years. The 5-year RSR for most lymphoid malignancies was improved: from 71.1% to 83.0% in HL, from 42.8% to 63.8% in mature B-cell neoplasms, and from 41.5% to 56.3% in precursor cell neoplasms.

Trends in the RSRs of several major subtypes that are clinically important and accessible in our database are shown in Fig. 3. Yearly improvement of survival outcome was observed in HL, diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), lymphoblastic lymphoma, and acute lymphoblastic leukemia. However, survival improvement was not evident in peripheral T-cell lymphomas or extranodal NK/T-cell lymphomas between 1993 and 2012.

Discussion

Here, we presented the first comprehensive epidemiologic analysis for lymphoid malignancies in the Korean population. The incidence of lymphoid malignancies increased yearly between 1999 and 2012. In most subtypes except precursor cell neoplasms, the incidences in adults and elderly patients were higher than those in pediatric patients. Relative survival improved during the study period in lymphoid malignancies. However, poor survival outcomes in elderly patients were observed in most subtypes except in indolent diseases such as marginal zone lymphoma.

The incidence of most subtypes in Korea was low, with an ASR less than one per 100,000 except for DLBCL (2.34) and plasma cell neoplasms (1.30). This incidence is quite low compared to data from other countries as we expected based on previous reports of differences in incidences of lymphoid malignancies between countries or ethnic groups (Table 3) [11,14,18,19]. The incidence of several subtypes, including follicular lymphoma (ASR, 0.18) and CLL (ASR, 0.18), is lower in Korea than in Western countries. In contrast, the incidence of extranodal NK/T-cell lymphoma, nasal type was relatively high (ASR, 0.22). CLL/small lymphocytic lymphoma (SLL) is the second most common subtype of mature B-cell malignancies in Europe (26%); however, it is rare in Korea (3.4%). Follicular lymphoma was also rare in Korea

Table 2. Five-year relative survival rates of lymphoid malignancies by age group in Korea

Site	Age (yr)	Year							
		1993-1997		1998-2002		2003-2007		2008-2012	
		Cases	Relative survival	Cases	Relative survival	Cases	Relative survival	Cases	Relative survival
Hodgkin's lymphoma	Total	473	71.1	649	72.9	862	79.1	1,135	83.0
	0-14	39	87.4	49	94.0	64	95.4	60	91.7
	15-34	167	83.1	226	88.8	306	89.8	420	93.4
	35-49	108	78.5	138	75.2	176	86.4	192	93.3
	50-64	100	53.3	141	58.3	180	74.4	247	80.0
	65-79	55	43.6	87	42.7	118	45.2	189	55.5
	≥ 80	< 5	-	8	-	18	-	27	37.0
Hodgkin's lymphoma, nodular lymphocyte predominant	Total	< 5	-	17	-	17	-	30	92.5
Classical Hodgkin's lymphoma	Total	469	71.0	632	72.8	845	79.0	1,105	82.7
	0-14	39	87.4	49	94.0	64	95.4	59	91.6
	15-34	167	83.1	223	88.7	299	89.6	409	93.2
	35-49	106	78.1	131	73.8	175	86.3	184	93.8
	50-64	98	53.3	136	58.9	173	74.4	239	80.2
	65-79	55	43.6	85	42.4	116	44.8	187	54.5
	≥ 80	< 5	-	8	-	18	-	27	37.0
Mature B-cell neoplasms	Total	4,339	42.8	8,413	47.9	13,590	58.7	19,601	63.8
	0-14	136	67.8	188	81.5	213	79.9	262	87.1
	15-34	495	57.7	704	68.8	996	84.8	1,164	87.6
	35-49	889	54.3	1,702	62.6	2,656	76.1	3,454	81.3
	50-64	1,676	40.3	3,097	47.0	4,602	62.3	6,638	69.9
	65-79	1,057	26.8	2,457	31.7	4,530	41.1	6,930	48.4
	≥ 80	86	28.4	265	21.1	593	25.2	1,153	29.6
Chronic lymphocytic leukemia/Small lymphocytic lymphoma	Total	306	53.1	414	53.7	469	63.0	601	73.7
	0-14	14	-	< 5	-	0	-	< 5	-
	15-34	24	-	15	-	< 5	-	9	-
	35-49	58	70.4	67	70.0	49	82.7	67	89.2
	50-64	111	57.0	156	58.5	163	67.3	199	88.0
	65-79	89	30.4	146	45.9	225	58.0	277	63.3
	≥ 80	10	-	26	6.6	28	41.4	47	45.3
Immunoproliferative diseases	Total	40	41.3	60	37.4	94	60.7	153	54.0

Table 2. Continued

Site	Age (yr)	Year							
		1993-1997		1998-2002		2003-2007		2008-2012	
		Cases	Relative survival	Cases	Relative survival	Cases	Relative survival	Cases	Relative survival
Mantle cell lymphoma	Total	40	60.8	118	53.0	237	41.4	355	52.4
	0-14	< 5	-	0	-	0	-	0	-
	15-34	5	-	8	-	5	-	< 5	-
	35-49	8	-	22	-	32	66.6	34	75.7
	50-64	12	-	53	45.9	91	43.9	138	54.1
	65-79	13	-	34	45.4	99	27.4	154	49.6
	≥ 80	< 5	-	< 5	-	10	-	27	0.0
Follicular lymphoma	Total	298	64.5	338	71.4	419	79.8	706	88.3
	0-14	7	-	7	-	< 5	-	< 5	-
	15-34	55	69.6	39	85.0	53	100.3	67	93.6
	35-49	80	71.6	103	84.7	117	81.4	207	95.1
	50-64	101	62.2	111	67.5	155	79.8	250	91.0
	65-79	51	57.8	70	49.8	84	63.2	161	74.6
	≥ 80	< 5	-	8	-	7	-	17	-
Diffuse large B-cell lymphoma	Total	2,213	49.5	4,413	52.9	6,377	59.1	8,574	61.5
	0-14	60	68.5	82	81.8	69	79.8	88	84.9
	15-34	347	55.4	499	65.6	538	80.6	611	81.5
	35-49	519	57.6	980	63.7	1,303	72.6	1,456	77.6
	50-64	783	49.0	1,532	53.7	2,058	64.2	2,701	70.2
	65-79	461	34.5	1,165	37.1	2,089	43.7	3,116	47.2
	≥ 80	43	36.5	155	28.8	320	23.0	602	27.1
Burkitt's lymphoma/Leukemia	Total	81	52.6	168	66.4	364	57.8	439	62.8
	0-14	47	70.3	90	83.4	126	79.4	155	87.0
	15-34	15	-	24	-	72	55.7	73	80.9
	35-49	5	-	15	-	49	59.8	81	47.8
	50-64	10	-	24	-	77	44.5	66	38.0
	65-79	< 5	-	13	-	36	12.6	58	24.3
	≥ 80	< 5	-	< 5	-	< 5	-	6	-
Marginal zone lymphoma	Total	59	90.3	548	85.7	2,165	95.0	3,808	98.2
	0-14	0	-	< 5	-	10	-	10	-
	15-34	16	-	79	92.8	279	97.8	364	99.2
	35-49	15	-	174	90.2	687	97.9	1,095	99.1
	50-64	21	-	188	88.2	747	96.6	1,513	97.9
	65-79	7	-	96	68.9	415	85.0	754	97.7
	≥ 80	0	-	7	-	27	86.5	72	89.3

Table 2. Continued

Site	Age (yr)	Year							
		1993-1997		1998-2002		2003-2007		2008-2012	
		Cases	Relative survival	Cases	Relative survival	Cases	Relative survival	Cases	Relative survival
B-Cell prolymphocytic leukemia	Total	0	-	0	-	6	-	25	57.0
Hairy cell leukemia	Total	11	-	13	-	16	-	26	69.8
Plasma cell neoplasms	Total	1,291	20.2	2,341	23.7	3,443	32.6	4,914	36.9
	0-14	< 5	-	< 5	-	< 5	-	< 5	-
	15-34	30	57.1	37	62.5	40	85.3	35	82.1
	35-49	194	29.5	326	37.1	401	50.6	498	52.0
	50-64	621	20.2	1,009	25.2	1,275	38.4	1,714	44.2
	65-79	417	12.2	904	16.1	1,538	23.1	2,301	29.5
	≥ 80	27	22.8	64	6.0	186	11.9	365	18.8
Mature T-cell and NK-cell neoplasms	Total	442	46.4	1,275	46.4	2,267	44.6	2,979	50.4
	0-14	32	56.4	51	82.4	104	67.4	94	74.8
	15-34	89	56.5	218	57.1	364	60.1	408	74.3
	35-49	126	46.8	322	52.1	554	50.6	667	60.3
	50-64	126	43.0	384	40.1	672	43.1	873	48.4
	65-79	59	32.8	272	34.7	505	26.6	791	32.8
	≥ 80	10	-	28	24.5	68	15.1	146	23.4
T lymphoma cutaneous	Total	63	59.8	128	72.6	217	82.5	419	87.7
	0-14	< 5	-	7	-	13	-	21	-
	15-34	11	-	31	77.7	58	88.2	107	95.6
	35-49	21	-	32	72.7	66	82.8	115	92.7
	50-64	15	-	30	69.7	49	84.6	95	91.6
	65-79	10	-	27	64.2	26	61.6	67	69.6
	≥ 80	< 5	-	< 5	-	5	-	14	-
Other T and NK-cell lymphomas	Total	379	44.2	1,147	43.5	2,050	40.5	2,560	44.2
	0-14	29	51.9	44	79.6	91	62.7	73	67.3
	15-34	78	51.6	187	53.7	306	54.8	301	66.7
	35-49	105	46.5	290	49.8	488	46.3	552	53.6
	50-64	111	41.2	354	37.5	623	39.9	778	43.0
	65-79	49	31.7	245	31.5	479	24.6	724	29.4
	≥ 80	7	-	27	25.3	63	13.4	132	24.8

Table 2. Continued

Site	Age (yr)	Year							
		1993-1997		1998-2002		2003-2007		2008-2012	
		Cases	Relative survival	Cases	Relative survival	Cases	Relative survival	Cases	Relative survival
Precursor cell neoplasms	Total	2,111	41.5	2,489	48.7	2,517	52.8	2,691	56.3
	0-14	1,161	61.6	1,286	71.3	1,254	77.8	1,189	82.7
	15-34	524	21.7	618	32.5	563	39.7	595	50.1
	35-49	203	13.0	289	21.0	321	24.6	407	33.0
	50-64	164	9.0	175	15.0	221	15.9	307	20.7
	65-79	57	6.8	113	3.2	142	6.2	174	13.5
	≥ 80	< 5	-	8	-	16	-	19	-
Lymphoblastic lymphoma	Total	101	43.0	222	45.8	249	51.8	294	54.4
	0-14	44	59.2	88	66.0	92	75.1	86	75.2
	15-34	35	31.6	91	36.4	93	47.5	113	54.4
	35-49	11	-	23	-	24	-	48	43.2
	50-64	8	-	11	-	28	29.9	23	-
	65-79	< 5	-	9	-	9	-	21	-
	≥ 80	0	-	0	-	< 5	-	< 5	-
Lymphoblastic leukemia	Total	2,010	41.4	2,267	49.0	2,268	52.9	2,397	56.5
	0-14	1,117	61.7	1,198	71.6	1,162	78.1	1,103	83.3
	15-34	489	21.0	527	31.8	470	38.2	482	49.2
	35-49	192	12.2	266	19.8	297	25.2	359	31.6
	50-64	156	7.4	164	15.3	193	13.9	284	20.9
	65-79	54	7.2	104	2.4	133	6.6	153	11.0
	≥ 80	< 5	-	8	-	13	-	16	-
Composite Hodgkin's and non-Hodgkin's lymphoma	Total	0	-	< 5	-	< 5	-	6	-
Unknown type lymphoid neoplasm	Total	3,227	47.1	2,957	52.7	1,935	52.1	1,435	50.2
	0-14	168	60.3	124	72.7	69	75.5	27	84.2
	15-34	522	52.8	369	65.6	194	76.5	98	81.4
	35-49	698	58.9	649	67.2	357	70.3	202	78.0
	50-64	1,064	45.6	897	54.5	507	60.7	329	66.2
	65-79	713	31.2	784	32.8	619	33.2	551	35.8
	≥ 80	62	21.3	134	23.0	189	16.8	228	13.5

Table 2. Continued

Site	Age (yr)	Year							
		1993-1997		1998-2002		2003-2007		2008-2012	
		Cases	Relative survival	Cases	Relative survival	Cases	Relative survival	Cases	Relative survival
All lymphoid malignancies	Total	10,592	45.3	15,784	49.9	21,173	56.7	27,847	61.7
	0-14	1,536	62.5	1,698	73.5	1,704	78.0	1,632	83.3
	15-34	1,797	48.1	2,135	58.6	2,423	70.6	2,686	78.0
	35-49	2,024	52.6	3,101	59.2	4,066	68.5	4,924	74.8
	50-64	3,130	40.9	4,694	47.0	6,182	58.7	8,394	66.0
	65-79	1,941	28.5	3,713	31.5	5,914	38.2	8,637	45.6
	≥ 80	164	25.4	443	21.1	884	22.4	1,574	26.6

-, statistic not displayed due to less than 25 cases; NK, natural killer.

compared to in European countries (3.4% vs. 11% of mature B-cell malignancies) [11]. The proportions of CLL/SLL and follicular lymphoma among B-cell non-Hodgkin's lymphoma (NHL) in the United States were 19.6% and 12.3%, respectively [14]. Although we cannot directly compare the ASRs from our data with those of other registry-based incidences, there are subtype-specific differences in the Korean population compared to foreign data. An increasing trend in the incidence of HL and NHL was observed in Korea, which is similar to Japan [19], but not the United States.

Comprehensive subtype-specific analysis in Asia is limited so far. A recent study performed in Hong Kong showed differences between Hong Kong and the United States [18]. The authors compared the incidences of lymphoid malignancies between the East Asian and white populations from Surveillance, Epidemiology, and End Results (SEER) data, and found that the age-adjusted incidence of most subtypes was < 1 per 100,000 in the Hong Kong population, except for DLBCL (3.26) and plasma cell neoplasms (1.99). The incidences of follicular lymphoma and CLL were 0.75 and 0.52, respectively, which was quite high compared to the incidences in our data (0.18 and 0.18). Rates in Asians from SEER data were generally intermediate compared to the rates in SEER Whites. Similar to our data, the incidence of extranodal T/NK-cell lymphoma, nasal type was much higher in Hong Kong (0.25) than in the United States (SEER White) (0.06). However, the number of Asian population in this analysis was relatively small compared to our data, with fewer than 10,000 cases in the Asian group, and survival data were lacking.

To our knowledge, this is the first population-based and subtype-specific survival analysis of hematologic malignancies in Asia. Comprehensive analysis based on subtypes defined by ICD-O-3 code is more useful than past population-based studies that divided lymphoid diseases in to broad categories such as 'non-Hodgkin's lymphoma' or 'leukemia' [20].

The multicenter retrospective analysis in Korea by Won et al. [21] previously showed that the overall survival rate of classical HL with a median follow-up of 30 months was 80.2%. It did not include pediatric patients under the age of 16 years. In our KCCR data, the 5-year survival rate was 82.7% in 2008-2012. The overall survival outcome of HL was favorable. However, the survival rate of elderly patients over 65 years significantly decreased to 37%-54.4%. The poor outcome of elderly patients may be due to unfavorable tumor biology and underlying comorbidities as well as the toxicity of current standard chemotherapy such as anthracyclines and bleomycin [22,23]. The introduction of less toxic but effective treatment would likely improve survival outcomes, especially in elderly patients, and the results of such treatment regimens could be evaluated in a future update of

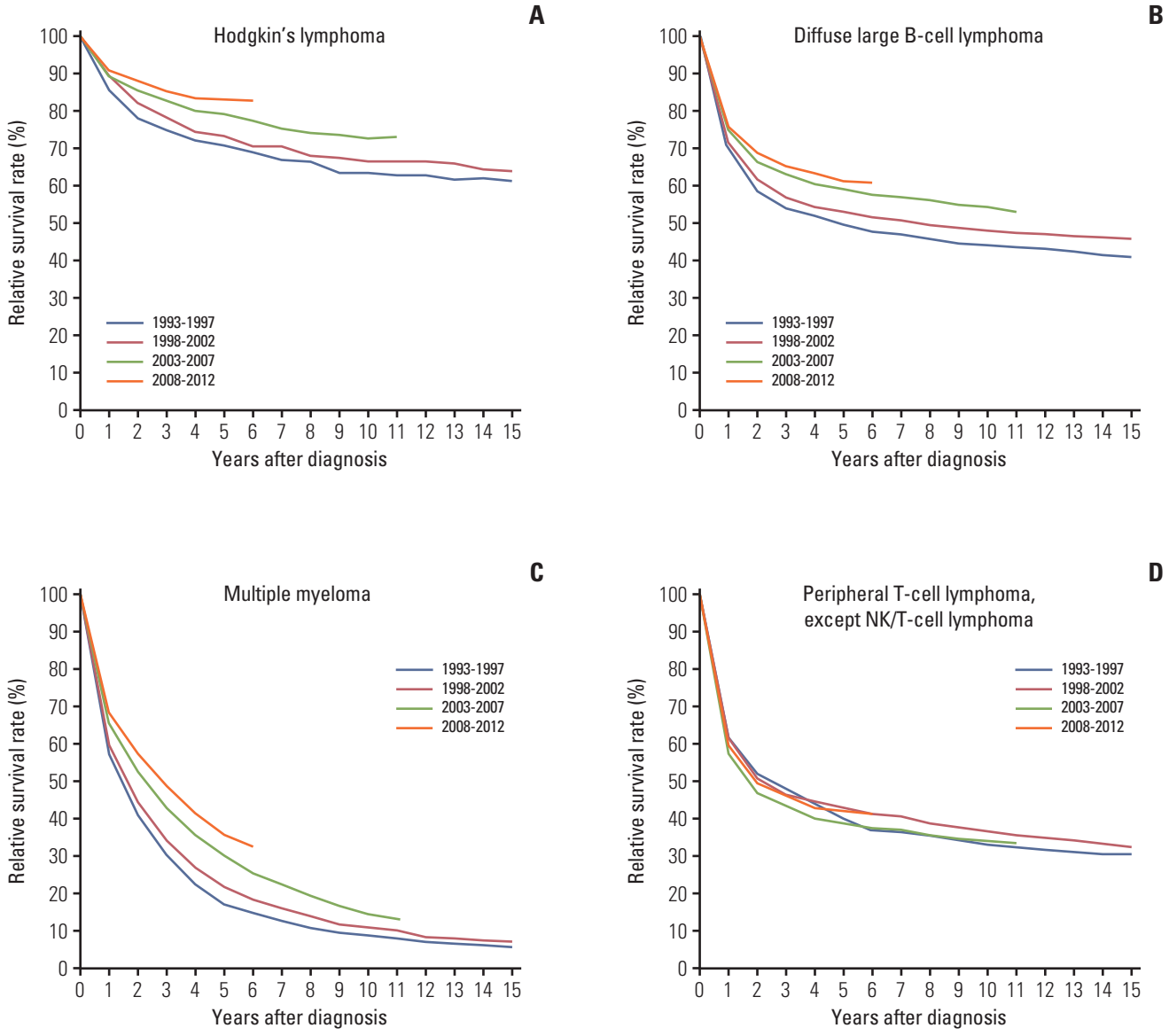


Fig. 3. Trend in relative survival rate of lymphoid malignances between 1993 and 2012 in Korea. ICD-O-3 codes are as follows. (A) Hodgkin's lymphoma 9659, 9650, 9661, 9662, 9651, 9663, 9664, 9665, 9667, 9652,9653, 9654, 9655. (B) Diffuse large B-cell lymphoma 9675, 9678, 9679, 9680, 96849684. (C) Multiple myeloma 9732. (D) Peripheral T-cell lymphoma, except NK/T-cell lymphoma 9702, 9705, 9714, 9716, 9717. *(Continued to the next page)*

KCCR analyses.

We also observed marked survival improvement in patients with DLBCL between the pre-rituximab and post-rituximab era: 5-year RSRs of 49.5% to 61.5% from 1993-1997 to 2008-2012, respectively. Rituximab, a monoclonal antibody that binds to CD20 on B cells and induces apoptosis of lymphoma cells, was approved in November 2003 by the Ministry of Food and Drug Safety (MFDS) in Korea. The influence of rituximab-containing chemoimmunotherapy on DLBCL survival has been reported [24]. In addition, rituximab has been approved for various indications in NHLs other than DLBCL in the United States [25]. In our data, survival rates of follicular lymphoma also increased during the study period. With the broadened indication of rituximab in Korea for other NHLs such as mantle cell lymphoma and marginal zone lymphoma, we can expect better outcomes in

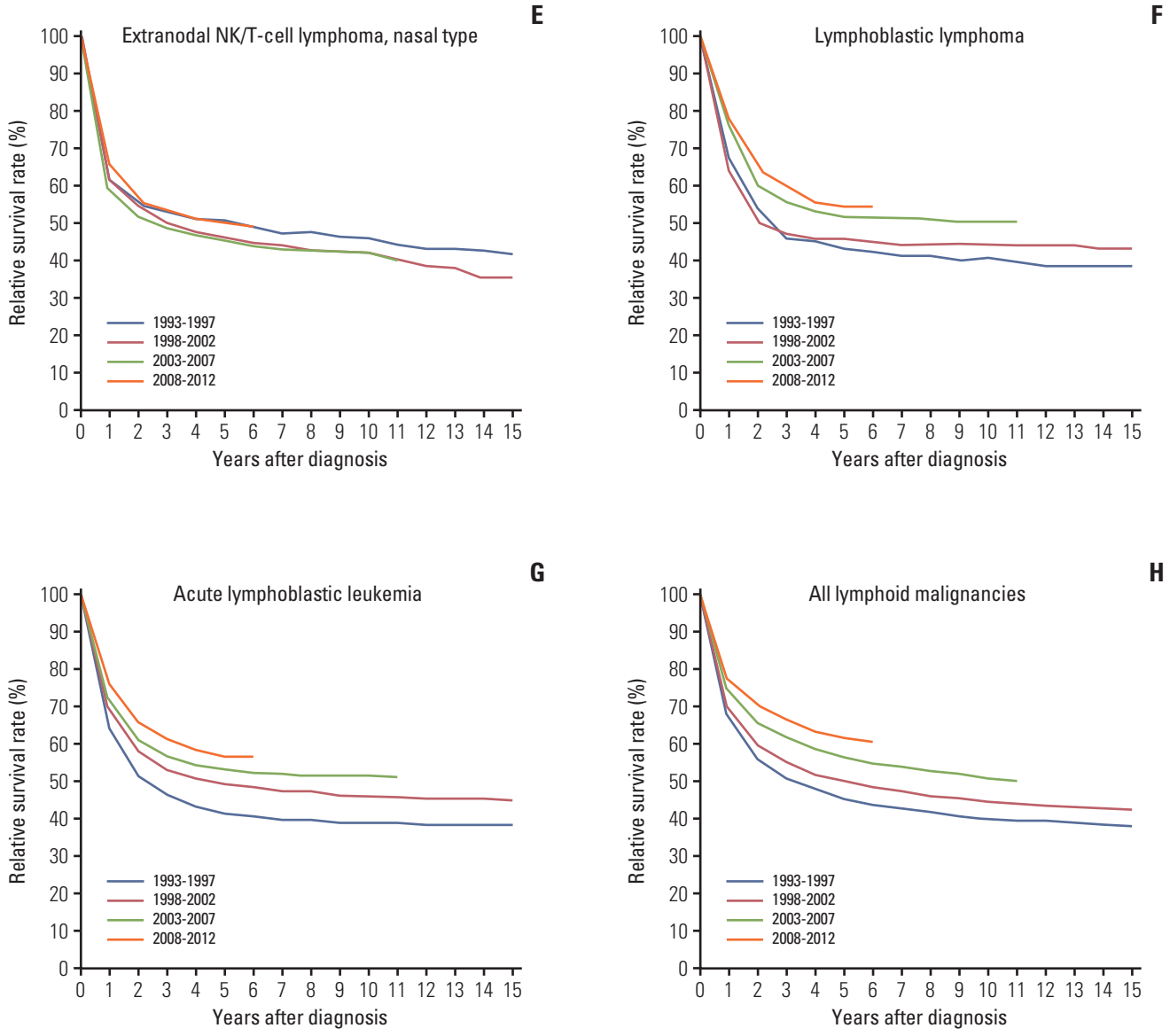


Fig. 3. *(Continued from the previous page)* (E) Extranodal NK/T-cell lymphoma, nasal type 9719. (F) Lymphoblastic lymphoma 9728, 9729, 9727. (G) Acute lymphoblastic leukemia 9836, 9837, 9835. (H) All lymphoid malignancies. ICD-O-3, International Classification of Diseases for Oncology, third edition.

the future data, although there were no significant improvements of survival in the present data.

For other T- and NK-cell lymphomas, except cutaneous T-cell lymphoma, there were no evident changes in survival rates during the study period (5-year RSR, 44.2% to 44.2% between 1993-1997 and 2008-2012, respectively). This result is in line with the unsatisfactory results of clinical trials for the disease categories, except for the paradigm shift in the management of extranodal NK/T-cell lymphoma, nasal type. In localized diseases, concomitant/sequential chemotherapy and radiotherapy became standard therapy because radiotherapy alone was not adequate due to systemic relapse [26]. For advanced cases, systemic chemotherapy containing L-asparaginase and drugs unaffected by P-glycoprotein was indicated [27]. In subtype-specific analyses, survival of extranodal NK/T-cell lymphoma, nasal type, improved, revealing a 5-year RSR of 49.9% for all age groups in 2008-2012 (n=869) compared to 45.8% in 2003-2007 (n=670) and 46.5% in 1998-2002 (n=314) (Fig. 3). The RSR in 1993-1997 seems to be superior, but this result might be due to a limi-

Table 3. International comparison of age-standardized incidence rates of lymphoid malignancies

	Europe (HAEMACARE)[a]	The United States (SEER White)[b]	The United States (SEER Asian)[b]	Hong Kong[b]	Japan[c]	KCCR[d]
	2000-2002	2001-2010	2001-2010	2001-2010	2008	1999-2012
HL	2.41	2.91	1.28	0.75	0.5	0.35
CLL/SLL	3.79	4.75	1.06	0.52	0.1	0.18
DLBCL	3.13	5.59	4.37	3.26	2.5	2.34
FL	1.92	3.17	1.33	0.75	0.1	0.18
MCL	NA	0.63	0.24	0.20	0.1	0.09
MZL	NA	1.53	1.18	0.74	0.5	0.79
BL	NA	0.42	0.28	0.27	0.12	0.16
PCN	4.62	4.03	2.54	1.99	1.5	1.30
Extranodal NK/T	NA	0.06	0.12	0.25	0.08	0.22
ALCL	NA	0.32	0.20	0.18	0.11	0.11
AITL	NA	0.10	0.13	0.12	0.12	0.10
PTCL-NOS	NA	0.30	0.28	0.27	0.25	0.26
ALL/LBL	1.42[e]	1.7[f]		NA	1.1	1.22
All lymphoid	24.50	28.55	16.11	11.22	NA	8.41

All rates expressed per 100,000 person-years. SEER, Surveillance, Epidemiology, and End Results; KCCR, Korea Central Cancer Registry; HL, Hodgkin's lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NA, not available; MZL, marginal zone lymphoma; BL, Burkitt's lymphoma/leukemia; PCN, plasma cell neoplasm; NK, natural killer; ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma. [a]Data from European HAEMACARE project [10], [b]Age-adjusted to the World Health Organization's World Standard Population (2000-2025) [21], [c]Age-standardized to the world population. Estimated values from the published figures [22], [d]Weighted averages of crude age-specific rates, calculated using Segi's world standard population (presented data), [e]This rate includes lymphoblastic lymphomas, [f]From SEER data including all ethnic groups. Age-adjusted to the 2,000 U.S. standard population [23].

tation of the registry; the registry did not cover the entire population at that time, so the number of cases was relatively insufficient (153 cases in 1993-1997). The survival benefits from the current therapy for extranodal NK/T-cell lymphoma, nasal type, needs to be confirmed in future analysis.

The standard treatment of MM also changed during the study period. Autologous stem cell transplantation was introduced in early 1990s. In addition, thalidomide, bortezomib, and lenalidomide were approved by MFDS in April 2006, March 2006, and December 2009, respectively. We found that the 5-year RSR of patients with plasma cell neoplasms changed from 20.2% to 36.9% from 1993 to 2012, respectively. This rate is still unsatisfactory, and it is lower than the RSR in the United States (48.5%) between 2006 and 2012 [14], but an increasing trend in survival rates in Korea is encouraging for such an 'incurable disease.'

The survival rates of acute lymphoblastic leukemia/lymphoma showed improving trends based on the year of diagnosis, with 5-year RSR of all age groups reaching 56.3% in 2008-2012. Age at diagnosis significantly influenced the survival of this disease. The 5-year RSR in pediatric patients (aged 0-14 years) is 82.7%, but it falls dramatically in young adults (50.1%, aged 15-34 years) and adults (33%, aged 35-49 years). Poor prognosis of adult acute lymphoblastic leukemia/lymphoma is historically well known, and the factors associated with this difference in outcome include the poorer biology of the leukemia, the lower compliance of patients (physically and emotionally), differences in the therapeutic approaches, and the lower rates of enrollment in clinical trials [28-30]. Efforts to improve outcomes in adults include development of pediatric-inspired chemotherapy protocols for young adults and the combination of tyrosine kinase inhibitors, such as imatinib and dasatinib with conventional chemotherapy for Philadelphia-positive disease. Well-designed and clinical trial-based treatment protocols for adult patients should be established in Korea.

We reported the subtype-specific incidence and survival of lymphoid malignancies. Our research showed increasing

incidence and survival rates based on the year of diagnosis in most subtypes. In addition, the survival rates of most subtypes (except for indolent disease) decreased dramatically with age. The strength of our study is that these data were analyzed in clinically meaningful disease categories. Additionally, this is a good example for refining and utilizing data from pre-existing cancer registry. If we can integrate more detailed information such as immunophenotypes, genetic abnormalities, and treatment information, to the registry, the quality of data on hematologic malignancies will improve. The qualified registry can provide practical evidence to determine whether advances in diagnosis and treatment can improve cancer survival.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (http://www.e-crt.org).

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

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