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Twenty-year incidence trend of hematologic malignancies in the Republic of Korea: 1999–2018

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Background
In this study, we presented the national cancer statistics on the incidence of hematologic malignancies in the Republic of Korea (ROK) over a period of 20 years, from 1999 to 2018.

Methods
We obtained data on the incidence of hematologic malignancies using the Korean Statistical Information Service (KOSIS). For each hematologic malignancy, the number of cases, crude incidence rate, and age-standardized incidence rate were calculated, and the statistical trends were confirmed by Poisson regression and Joinpoint regression analysis.

Results
All the investigated hematologic malignancies showed a statistically significant increase in incidence over 20 years. The 20-year trend of the age-standardized incidence rate was as follows: non-Hodgkin lymphoma [average annual percent change (AAPC)=2.26%, *P*-trend <0.05], leukemia (AAPC=0.94%, *P*-trend <0.05), myeloid leukemia (AAPC=1.44%, *P*-trend <0.05), multiple myeloma (AAPC=3.05%, *P*-trend <0.05), myeloproliferative disorders (AAPC=9.87%, *P*-trend <0.05), myelodysplastic syndrome (AAPC=7.59%, *P*-trend <0.05), malignant immunoproliferative diseases (AAPC=11.82%, *P*-trend <0.05), lymphoid leukemia (AAPC=2.21%, *P*-trend <0.05), and Hodgkin lymphoma (AAPC=4.04%, *P*<0.05).

Conclusion
It was confirmed that the incidence of hematologic malignancies has increased significantly in the ROK over the past 20 years. This study can be used as foundational data source for future studies. In addition, it can aid in the necessary actions of predicting future incidences and establishing future healthcare policies.

Key Words Epidemiology, Hematologic neoplasms, Neoplasms, Registries, Statistics

INTRODUCTION

Since the national causes of death statistics were officially established in 1983, cancer has been the number one cause of death in the Republic of Korea (ROK) to date [1]. With the aging of the population, the incidence of cancer has also been increasing rapidly [2]. The Korea Central Cancer Registry (KCCR) registers cancer-related data and publishes books on cancer statistics every year. However, since the cancer statistics book mainly describes only the most common types of cancers, it is up to each researcher to analyze the statistical data of detailed cancers. This study intends to provide statistics on the incidence of hematologic malignancies over the past 20 years based on open national statistical data. The results of this study will be used as foundational data for future research and policy establishment on hematologic malignancies.

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MATERIALS AND METHODS

Data collection

We obtained data on hematologic malignancies from 1999 to 2018 through the Korean Statistical Information Service (KOSIS). KOSIS is a national statistical database operated by Statistics Korea. As a gateway for Korea's official statistics, KOSIS offers a convenient one-stop service to a full range of major domestic statistics. Currently, official statistics produced by over 120 statistical agencies covering more than 500 subject matter are available on the KOSIS. Data are provided in an open form and can be easily accessed by anyone [3]. The data we obtained were as follows: the number of incidences of hematologic malignancies by 5-year age groups and sex, and the population structure for each year. The cancer data registered in the KOSIS were created by the KCCR, Ministry of Health and Welfare.

Malignancy classification

Hematologic malignancies were categorized according to the International Classification of Diseases for Oncology 3rd edition (ICD-O-3) [4]. For consistent comparison and convenience, these malignancies were converted to the International Classification of Diseases, 10th edition (ICD-10) [5]. Diseases not classified as malignant according to ICD-10 (myeloproliferative disorders and myelodysplastic syndromes) were referred to using ICD-O-3 codes without

Table 1. The classification of hematologic malignancies according to the Republic of Korea's Cancer Control Act and Statistics Act.

Abbreviation	ICD-10 code (or ICD-O-3 code)	
Non-Hodgkin lymphoma	ICD-10 C82–C86, C96	Follicular lymphoma. Follicle center lymphoma. Other types of follicular lymphoma. Follicular lymphoma, unspecified. Small cell B-cell lymphoma. Mantle cell lymphoma. Diffuse large B-cell lymphoma. Lymphoblastic (diffuse) lymphoma. Burkitt lymphoma. Other non-follicular lymphoma. Non-follicular (diffuse) lymphoma, unspecified. Mature T/NK-cell lymphomas. Mycosis fungoides. Sézary disease. Peripheral T-cell lymphoma, not classified. Anaplastic large cell lymphoma. Cutaneous T-cell lymphoma, unspecified. Other mature T/NK-cell lymphomas. Mature T/NK-cell lymphomas, unspecified. Unspecified B-cell lymphoma. Mediastinal (thymic) large B-cell lymphoma. Other specified types of non-Hodgkin lymphoma. Non-Hodgkin lymphoma, unspecified. Other specified types of T/NK-cell lymphoma. Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis. Malignant mast cell neoplasm. Sarcoma of dendritic cells (accessory cells). Multifocal and unisystemic Langerhans-cell histiocytosis. Unifocal Langerhans-cell histiocytosis. Histiocytic sarcoma. Other specified.
Leukemia	ICD-10 C91–95	See myeloid leukemia, lymphoid leukemia, and leukemia unspecified.
Myeloid leukemia	ICD-10 C92–C94	Acute myeloblastic leukemia. Chronic myeloid leukemia. Myeloid sarcoma. Acute promyelocytic leukemia. Acute myelomonocytic leukemia. Acute myeloid leukemia. Other myeloid leukemia. Myeloid leukemia, unspecified. Acute monoblastic/monocytic leukemia. Chronic myelomonocytic leukemia. Juvenile myelomonocytic leukemia. Other monocytic leukemia. Monocytic leukemia, unspecified. Acute erythroid leukemia. Acute megakaryoblastic leukemia. Mast cell leukemia. Acute panmyelosis with myelofibrosis.
Multiple myeloma	ICD-10 C90	Multiple myeloma. Plasma cell leukemia. Extramedullary plasmacytoma. Solitary plasmacytoma.
Myeloproliferative disorders	ICD-O-3 M995_/3, M996_/3, M997_/3	Polycythemia vera. Chronic myeloproliferative disease. Essential thrombocythemia. Osteomyelofibrosis. Chronic eosinophilic leukemia.
Myelodysplastic syndrome	ICD-O-3 M9980/3 ~M9983/3, M9985/3 ~M9989/3	Myelodysplastic syndromes.
Malignant immunoproliferative diseases	ICD-10 C88	Waldenström macroglobulinemia. Heavy chain disease. Immunoproliferative small intestinal disease. Extranodalmarginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]. Other malignant immunoproliferative diseases. Malignant immunoproliferative disease, unspecified.
Lymphoid leukemia	ICD-10 C91	Acute lymphoblastic leukemia. Chronic lymphocytic leukemia of B-cell type. Prolymphocytic leukemia of B-cell type. Hairy cell leukemia. Adult T-cell lymphoma/leukemia. Prolymphocytic leukemia of T-cell type. Mature B-cell leukemia Burkitt-type. Other lymphoid leukemia. Lymphoid leukemia, unspecified.
Hodgkin lymphoma	ICD-10 C81	Hodgkin lymphoma. Other Hodgkin lymphoma. Hodgkin lymphoma, unspecified.
Leukemia unspecified	ICD-10 C95	Acute leukemia of unspecified cell type. Chronic leukemia of unspecified cell type. Leukemia, unspecified.

conversion. The classification of hematologic malignancies according to the ICD-10 was as follows: non-Hodgkin lymphoma (C82–86, C96), leukemia (C91–95), myeloid leukemia (C92–94), multiple myeloma (C90), myeloproliferative disorders (ICD-O-3 M995_/3, M996_/3, M997_/3), myelodysplastic syndrome (ICD-O-3 M9980/3, M9981/3, M9982/3, M9983/3, M9985/3, M9986/3, M9987/3, M9988/3, M9989/3), malignant immunoproliferative diseases (C88), lymphoid leukemia (C91), Hodgkin lymphoma (C81), and leukemia of unspecified cell type (C95) (Table 1).

Table 2. The incidence case number of non-Hodgkin lymphoma and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	1,252	851	2,103	5.16[b]	44.58964	45.47851	2.26[b]	1.023[b]
2000	1,222	816	2,038		42.87447	42.87447		
2001	1,332	905	2,237		46.72385	45.78075		
2002	1,322	919	2,241		46.56551	44.58582		
2003	1,375	981	2,356		48.77000	45.65773		
2004	1,511	1,057	2,568		52.96449	48.58076		
2005	1,505	1,091	2,596		53.32453	47.61164		
2006	1,651	1,121	2,772		56.70216	49.38565		
2007	1,741	1,194	2,935		59.73904	50.59199		
2008	1,745	1,256	3,001		60.74327	50.12326		
2009	1,876	1,362	3,238		65.20764	52.63546		
2010	1,954	1,429	3,383		67.82303	53.64297		
2011	2,110	1,551	3,661		73.05712	56.72628		
2012	2,194	1,580	3,774		74.96227	56.77698		
2013	2,314	1,691	4,005		79.21446	57.80355		
2014	2,400	1,713	4,113		81.02333	58.60555		
2015	2,560	1,884	4,444		87.21982	61.06796		
2016	2,805	2,019	4,824		94.37917	64.58155		
2017	2,736	2,080	4,816		94.00613	63.41746		
2018	3,001	2,215	5,216		101.67467	66.87682		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

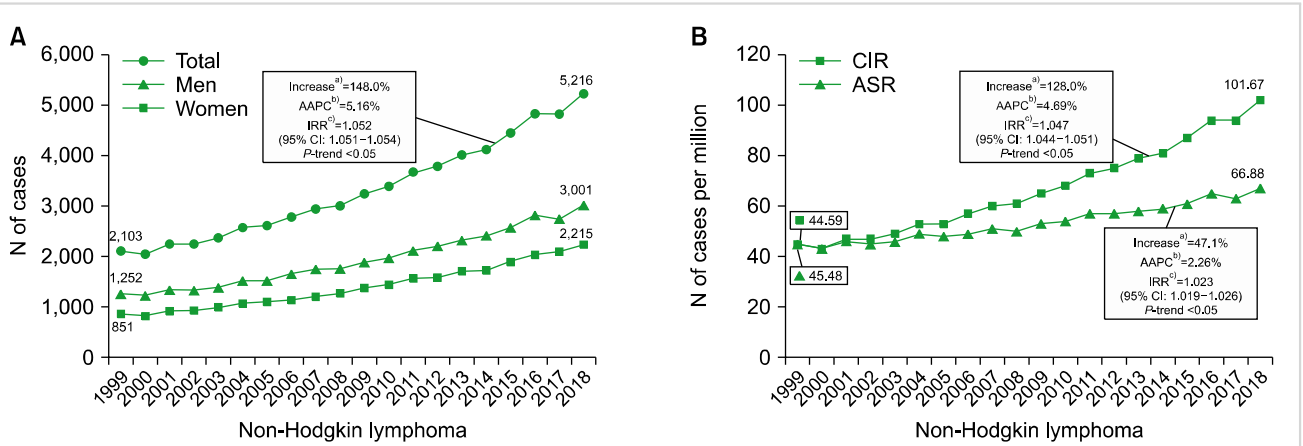

Fig. 1. Annual incidence of non-Hodgkin lymphoma in the Republic of Korea. Number of non-Hodgkin lymphoma cases **(A)**. Crude and age-standardized incidence rate of non-Hodgkin lymphoma per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Statistical analysis

From the collected data, the number of incidence cases of each hematologic malignancy by year was determined. The average annual percent change (AAPC) was analyzed using the Joinpoint regression model which is a trend analysis software developed by the US National Cancer Institute [6]. This method describes changes in data trends by connecting several different line segments on a logarithmic scale at Joinpoints. Tests of significance were performed using the Monte Carlo permutation method. An AAPC for each line segment and the corresponding 95% confidence interval (CI) were estimated. The AAPC is tested to determine whether a difference exists from the null hypothesis of no change. In the final model, each Joinpoint informs a statistically significant change in trends, and each of these trends is described by an AAPC [7]. The crude incidence rate (CIR) for each year and the age-standardized incidence rate (ASR) was calculated by defining the 2000 mid-year population (the population count as of July 1, 2000) as the standard population [CIR=(the number of new patients/mid-year population) ×1,000,000]. From 1998 to 2018, each incidence rate ratio (IRR) was calculated according to the one-year increase through Poisson regression, and the 95% CI and *P*-value were calculated. The CIRs and ASRs were rounded to six decimal places. Poisson regression was performed by converting the number of cases per 10 million people into an integer. Poisson regression analyses were performed using SPSS (version 27.0, IBM Corp., Armonk, NY, USA), and the significance level was set at $P<0.05$.

RESULTS

Non-Hodgkin lymphoma

The number of newly diagnosed NHL cases increased by 148.0%, from 2,103 in 1999 to 5,216 in 2018. The AAPC in incidence cases during this period was 5.16%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.052 (95% CI, 1.051–1.054; $P<0.001$). The CIR per million population increased by 128.0% from 44.59 in 1999 to 101.67 in 2018. Within a one-year increase, the IRR increased significantly to 1.047 (95% CI, 1.044–1.051; $P<0.001$). The ASR per million population increased by 47.1% from 45.48 in 1999 to 66.88 in 2018. Within a one-year increase, the IRR increased significantly to 1.023 (95% CI, 1.019–1.026; $P<0.001$). The AAPC in the ASR during this period was 2.26%, and the trend was statistically significant ($P<0.05$) (Table 2, Fig. 1).

Leukemia

The number of newly diagnosed leukemia cases increased by 64.5%, from 2,124 in 1999 to 3,494 in 2018. The AAPC in incidence cases during this period was 2.89%, and the trend was statistically significant. Within a one-year increase,

Table 3. The incidence case number of leukemia and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	1,188	936	2,124	2.89[b]	45.03490	45.45859	0.94[b]	1.009[b]
2000	1,105	901	2,006		42.20127	42.20127		
2001	1,210	998	2,208		46.11813	45.74454		
2002	1,333	987	2,320		48.20705	47.29788		
2003	1,247	1,034	2,281		47.21748	45.74993		
2004	1,321	1,051	2,372		48.92203	46.79217		
2005	1,332	1,015	2,347		48.20981	45.83396		
2006	1,342	1,102	2,444		49.99281	47.05533		
2007	1,388	1,090	2,478		50.43725	46.91184		
2008	1,455	1,145	2,600		52.62663	48.27268		
2009	1,504	1,212	2,716		54.69548	48.90856		
2010	1,572	1,186	2,758		55.29291	48.55470		
2011	1,618	1,283	2,901		57.89093	50.27748		
2012	1,621	1,246	2,867		56.94670	48.31113		
2013	1,754	1,317	3,071		60.74097	50.21212		
2014	1,785	1,324	3,109		61.24520	50.30621		
2015	1,855	1,433	3,288		64.53168	52.86386		
2016	1,995	1,438	3,433		67.16495	54.19071		
2017	1,934	1,454	3,388		66.13222	51.23865		
2018	2,037	1,457	3,494		68.10799	52.44745		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

the IRR increased significantly to 1.029 (95% CI, 1.028–1.031; $P<0.001$). The CIR per million population increased by 51.3% from 45.03 in 1999 to 68.11 in 2018. Within a one-year increase, the IRR increased significantly to 1.025 (95% CI, 1.021–1.028; $P<0.001$). The ASR per million population increased by 15.4% from 45.46 in 1999 to 52.45 in 2018. Within a one-year increase, the IRR increased significantly to 1.009 (95% CI, 1.006–1.013; $P<0.001$). The AAPC in the ASR during this period was 0.94%, and the trend was statistically significant ($P<0.05$) (Table 3, Fig. 2).

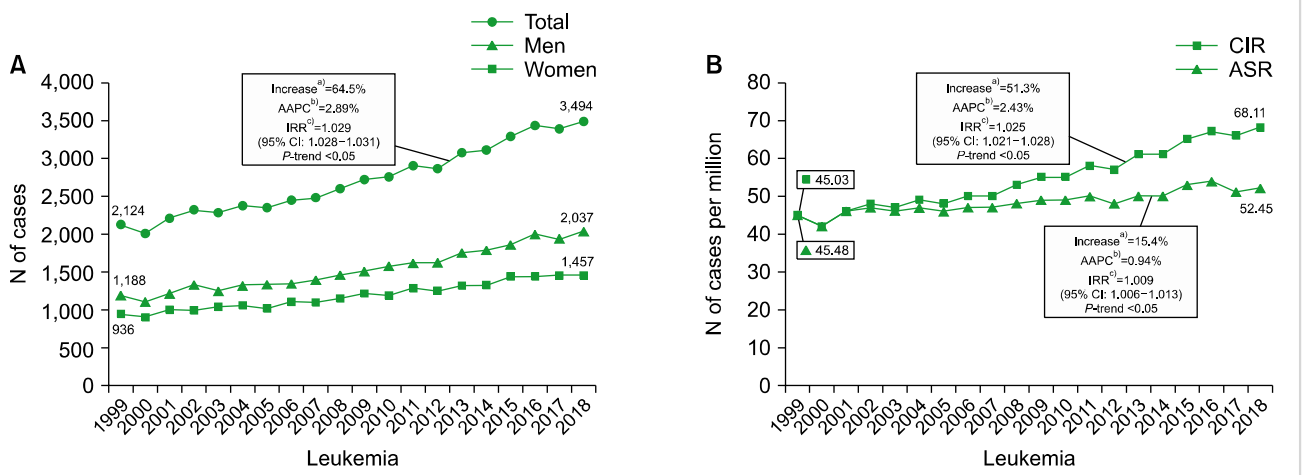

Fig. 2. Annual incidence of leukemia in the Republic of Korea. Number of leukemia cases **(A)**. Crude and age-standardized incidence rate of leukemia per million using the 2000 Korean standard population **(B)**. [a]Comparing to 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 4. The incidence case number of myeloid leukemia and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	696	526	1,222	3.81[b]	25.90991	26.21218	1.44[b]	1.014[b]
2000	630	542	1,172		24.65597	24.65597		
2001	720	607	1,327		27.71683	27.39936		
2002	806	588	1,394		28.96579	28.20531		
2003	768	641	1,409		29.16678	27.92552		
2004	853	658	1,511		31.16408	29.40229		
2005	812	657	1,469		30.17478	28.04162		
2006	839	677	1,516		31.01027	28.33077		
2007	873	676	1,549		31.52837	28.48103		
2008	947	743	1,690		34.20731	30.20098		
2009	980	755	1,735		34.93986	30.13031		
2010	1,050	748	1,798		36.04665	30.26675		
2011	1,084	841	1,925		38.41435	32.02027		
2012	1,060	787	1,847		36.68662	29.72320		
2013	1,238	879	2,117		41.87191	32.97980		
2014	1,231	862	2,093		41.23069	32.13509		
2015	1,285	964	2,249		44.13983	34.03683		
2016	1,384	914	2,298		44.95923	33.80285		
2017	1,345	972	2,317		45.22678	32.37206		
2018	1,435	990	2,425		47.27014	34.03950		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

Myeloid leukemia

The number of newly diagnosed myeloid leukemia cases increased by 98.4%, from 1,222 in 1999 to 2,425 in 2018. The AAPC in incidence cases during this period was 3.81%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.038 (95% CI, 1.036–1.040; $P<0.001$). The CIR per million population increased by 82.4% from 25.91 in 1999 to 47.27 in 2018. Within a one-year increase, the IRR increased significantly to 1.034 (95% CI, 1.029–1.038; $P<0.001$). The ASR per million pop-

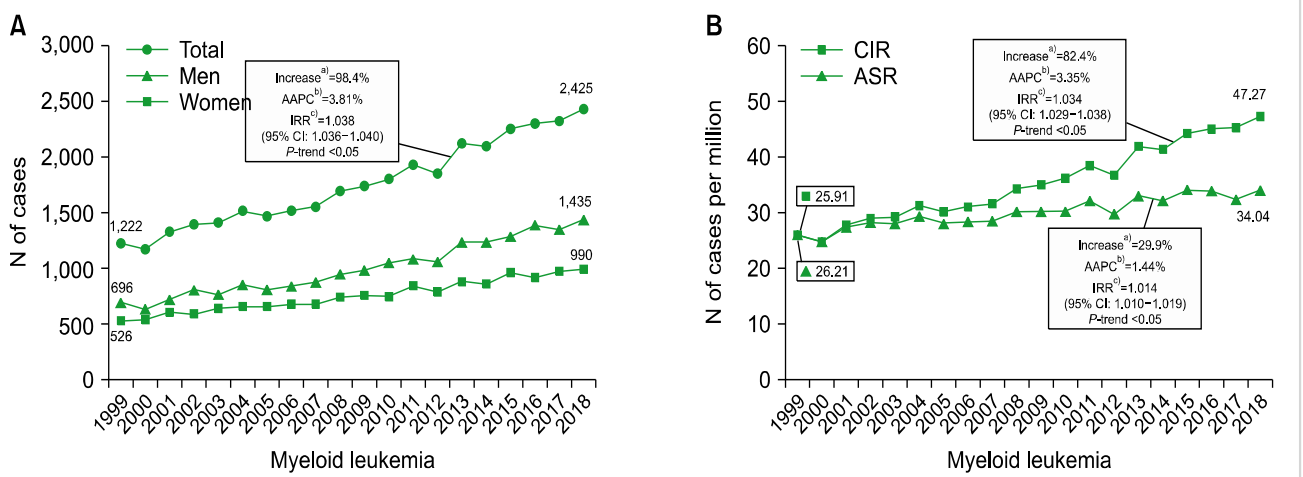

Fig. 3. Annual incidence of myeloid leukemia in the Republic of Korea. Number of myeloid leukemia cases **(A)**. Crude and age-standardized incidence rate of myeloid leukemia per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 5. The incidence case number of multiple myeloma and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	257	212	469	7.33[b]	9.94415	10.22460	3.05[b]	1.030[b]
2000	275	217	492		10.35046	10.35046		
2001	313	251	564		11.78017	11.46171		
2002	328	239	567		11.78164	11.07893		
2003	331	285	616		12.75141	11.55148		
2004	362	315	677		13.96299	12.21290		
2005	407	387	794		16.30958	13.71200		
2006	386	384	770		15.75060	12.94935		
2007	459	430	889		18.09472	14.16175		
2008	492	425	917		18.56101	14.26485		
2009	575	462	1,037		20.88336	15.34012		
2010	569	510	1,079		21.63200	15.12175		
2011	610	469	1,079		21.53199	14.62146		
2012	706	589	1,295		25.72235	17.05821		
2013	704	646	1,350		26.70150	16.71056		
2014	771	649	1,420		27.97304	16.87157		
2015	772	704	1,476		28.96860	16.91477		
2016	845	708	1,553		30.38368	17.22267		
2017	864	779	1,643		32.07061	17.32490		
2018	927	792	1,719		33.50820	17.51734		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

ulation increased by 29.9% from 26.21 in 1999 to 34.04 in 2018. Within a one-year increase, the IRR increased significantly to 1.014 (95% CI, 1.010–1.019; $P<0.001$). The AAPC in the ASR during this period was 1.44%, and the trend was statistically significant ($P<0.05$) (Table 4, Fig. 3).

Multiple myeloma

The number of newly diagnosed MM cases increased by 266.5% from 469 in 1999 to 1,719 in 2018. The AAPC in incidence cases during this period was 7.33%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.071 (95% CI, 1.069–1.074;

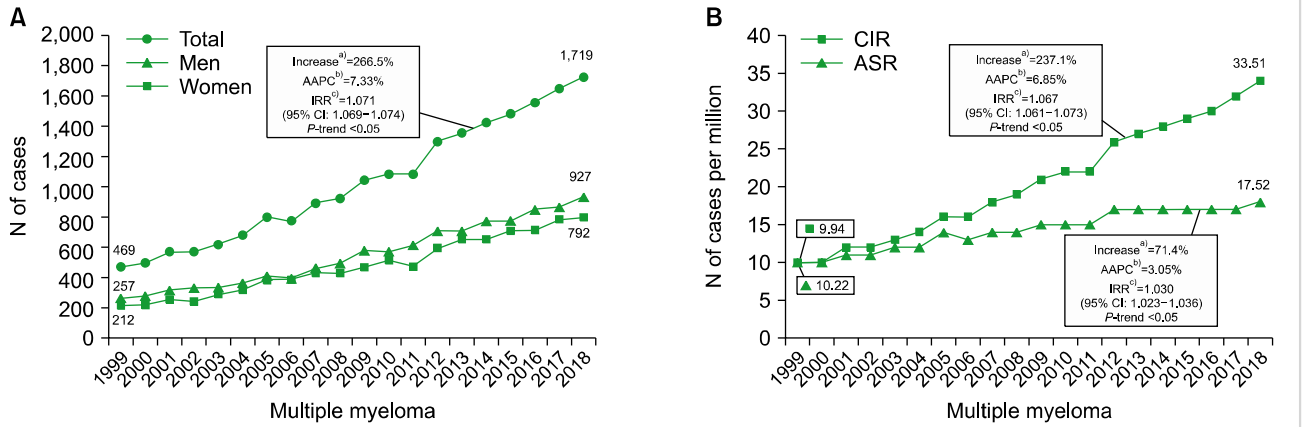

Fig. 4. Annual incidence of multiple myeloma in the Republic of Korea. Number of multiple myeloma cases **(A)**. Crude and age-standardized incidence rate of multiple myeloma per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 6. The incidence case number of myeloproliferative disorders and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	55	55	110	13.28[b]	2.33232	2.38291	9.87[b]	1.080[b]
2000	65	75	140		2.94525	2.94525		
2001	86	92	178		3.71786	3.64427		
2002	135	116	251		5.21550	4.96014		
2003	200	154	354		7.32792	6.76541		
2004	194	169	363		7.48680	6.68212		
2005	283	242	525		10.78404	9.50474		
2006	282	245	527		10.77996	9.23111		
2007	365	287	652		13.27082	11.12117		
2008	370	327	697		14.10798	11.45405		
2009	409	402	811		16.33212	12.78754		
2010	431	401	832		16.68010	12.76728		
2011	506	418	924		18.43889	13.80286		
2012	477	444	921		18.29366	13.27581		
2013	509	456	965		19.08663	13.55994		
2014	595	481	1,076		21.19647	14.81846		
2015	621	511	1,132		22.21711	15.05132		
2016	640	620	1,260		24.65128	16.13719		
2017	723	584	1,307		25.51204	16.36598		
2018	809	739	1,548		30.17492	19.00324		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

$P<0.001$). The CIR per million population increased by 237.1% from 9.94 in 1999 to 33.51 in 2018. Within a one-year increase, the IRR increased significantly to 1.067 (95% CI, 1.061–1.073; $P<0.001$). The ASR per million population increased by 71.4% from 10.22 in 1999 to 17.52 in 2018. Within a one-year increase, the IRR increased significantly to 1.030 (95% CI, 1.023–1.036; $P<0.001$). The AAPC in the ASR during this period was 3.05%, and the trend was statistically significant ($P<0.05$) (Table 5, Fig. 4).

Myeloproliferative disorders

The number of newly diagnosed myeloproliferative dis-

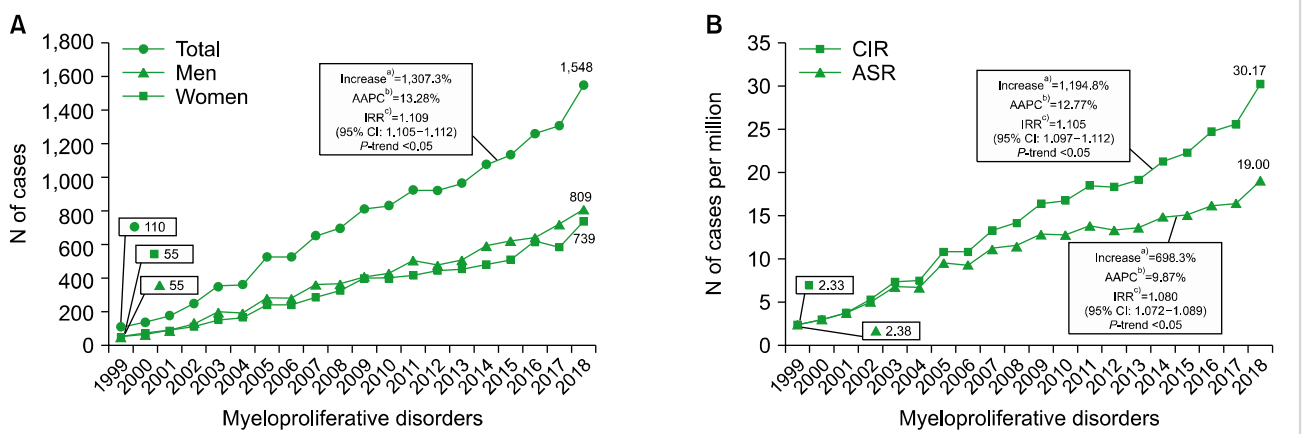

Fig. 5. Annual incidence of myeloproliferative disorders in the Republic of Korea. Number of myeloproliferative disorders cases **(A)**. Crude and age-standardized incidence rate of myeloproliferative disorders per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 7. The incidence case number of myelodysplastic syndrome and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	88	51	139	11.49[b]	2.94720	2.99630	7.59[b]	1.064[b]
2000	90	77	167		3.51327	3.51327		
2001	129	91	220		4.59510	4.48965		
2002	165	97	262		5.44407	5.22327		
2003	234	160	394		8.15593	7.54460		
2004	253	165	418		8.62117	7.76107		
2005	280	190	470		9.65429	8.59289		
2006	299	190	489		10.00265	8.63391		
2007	314	250	564		11.47967	9.47229		
2008	377	268	645		13.05545	10.52395		
2009	446	280	726		14.62037	11.37083		
2010	479	305	784		15.71778	11.62239		
2011	486	390	876		17.48103	12.72050		
2012	521	318	839		16.66490	11.46736		
2013	543	396	939		18.57238	12.55258		
2014	600	386	986		19.42354	12.77860		
2015	626	407	1,033		20.27410	13.04959		
2016	742	428	1,170		22.89047	13.84107		
2017	707	451	1,158		22.60363	13.39331		
2018	828	537	1,365		26.60773	15.30694		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

orders increased by 1,307.3% from 110 in 1999 to 1,548 in 2018. The AAPC in incidence cases during this period was 13.28%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.109 (95% CI, 1.105–1.112; $P<0.001$). The CIR per million population increased by 1,194.8% from 2.33 in 1999 to 30.17 in 2018. Within a one-year increase, the IRR increased significantly to 1.105 (95% CI, 1.097–1.112; $P<0.001$). The ASR per million population increased by 698.3% from 2.38 in 1999 to 19.00 in 2018. Within a one-year increase, the IRR increased significantly to 1.080 (95% CI, 1.072–1.089; $P<0.001$). The AAPC in the ASR during this

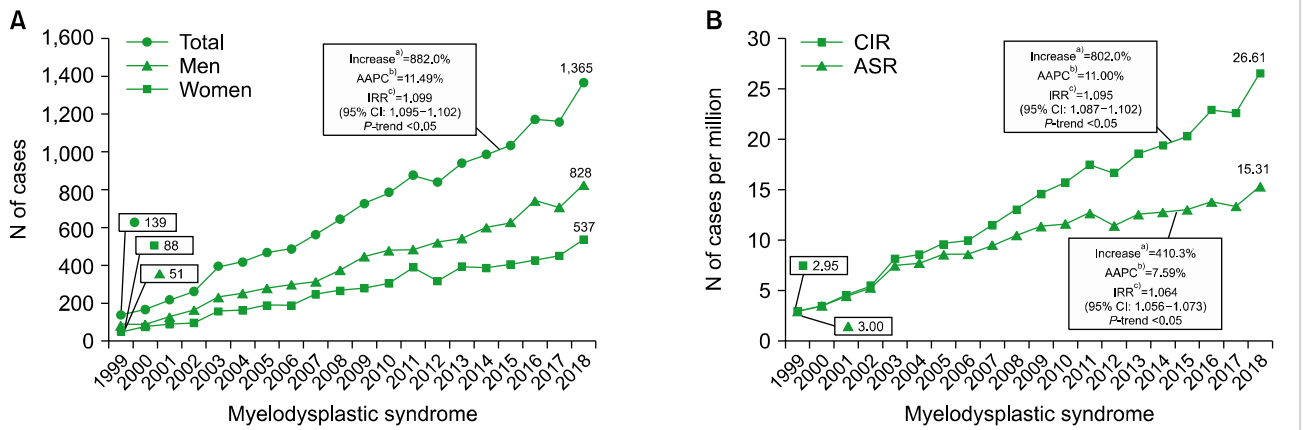

Fig. 6. Annual incidence of myelodysplastic syndrome in the Republic of Korea. Number of myelodysplastic syndrome cases **(A)**. Crude and age-standardized incidence rate of myelodysplastic syndrome per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 8. The incidence case number of malignant immunoproliferativediseases and trend in crude incidence rates and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	45	50	95	14.76[b]	2.01427	2.04994	11.82[b]	1.090[b]
2000	39	39	78		1.64093	1.64093		
2001	49	50	99		2.06780	2.00910		
2002	98	96	194		4.03111	3.87658		
2003	165	171	336		6.95531	6.50023		
2004	175	174	349		7.19806	6.56316		
2005	198	252	450		9.24347	8.26204		
2006	212	272	484		9.90038	8.66932		
2007	227	250	477		9.70887	8.37596		
2008	251	327	578		11.69930	9.91273		
2009	348	386	734		14.78147	12.09930		
2010	315	416	731		14.65523	11.92735		
2011	348	480	828		16.52316	12.85307		
2012	413	471	884		17.55873	13.55260		
2013	412	509	921		18.21636	13.44186		
2014	437	507	944		18.59616	13.78266		
2015	459	492	951		18.66473	13.50497		
2016	592	603	1,195		23.37958	16.40845		
2017	574	609	1,183		23.09162	15.98123		
2018	601	710	1,311		25.55512	17.46422		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

period was 9.87%, and the trend was statistically significant ($P<0.05$) (Table 6, Fig. 5).

Myelodysplastic syndrome

The number of newly diagnosed myelodysplastic syndromes increased by 882.0% from 139 in 1999 to 1,365 in 2018. The AAPC in incidence cases during this period was 11.49%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.099 (95% CI, 1.095–1.102; $P<0.001$). The CIR per million population increased by 802.0% from 2.95 in 1999 to 26.61 in 2018. Within a one-year increase, the IRR increased sig-

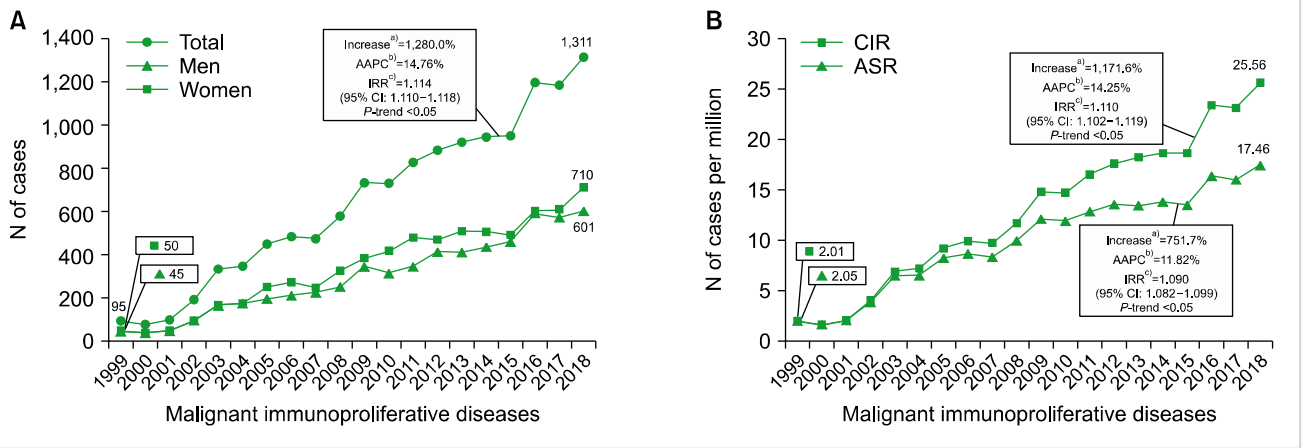

Fig. 7. Annual incidence of malignant immunoproliferative diseases in the Republic of Korea. Number of malignant immunoproliferative diseases cases **(A)**. Crude and age-standardized incidence rate of malignant immunoproliferative diseases per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 9. The incidence case number of lymphoid leukemia and trend in crude incidence rates and age-standardized incidence rates per million populationin the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	316	234	550	2.77[b]	11.66158	11.61904	2.21[b]	1.022[b]
2000	280	216	496		10.43461	10.43461		
2001	316	228	544		11.36244	11.42331		
2002	335	222	557		11.57385	11.76349		
2003	303	248	551		11.40589	11.63373		
2004	301	232	533		10.99302	11.25614		
2005	328	226	554		11.37973	11.87085		
2006	331	272	603		12.33456	12.82142		
2007	344	260	604		12.29383	12.87728		
2008	349	260	609		12.32678	12.97963		
2009	373	289	662		13.33152	13.75206		
2010	361	281	642		12.87094	13.44971		
2011	363	305	668		13.33028	13.76827		
2012	388	312	700		13.90397	14.16193		
2013	371	314	685		13.54854	13.57623		
2014	434	326	760		14.97149	15.01366		
2015	456	359	815		15.99553	16.01589		
2016	481	383	864		16.90373	16.92706		
2017	463	365	828		16.16218	16.11329		
2018	465	352	817		15.92565	15.53953		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

nificantly to 1.095 (95% CI, 1.087–1.102; $P<0.001$). The ASR per million population increased by 410.3% from 3.00 in 1999 to 15.31 in 2018. Within a one-year increase, the IRR increased significantly to 1.064 (95% CI, 1.056–1.073; $P<0.001$). The AAPC in the ASR during this period was 7.59%, and the trend was statistically significant ($P<0.05$) (Table 7, Fig. 6).

Malignant immunoproliferative diseases

The number of newly diagnosed malignant immunoproliferative diseases increased by 1,280.0%, from 95 in 1999 to 1,311 in 2018. The AAPC in incidence cases during this period was 14.76%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.114 (95% CI, 1.110–1.118; $P<0.001$). The CIR per million population increased by 1,171.6% from 2.01 in 1999 to 25.56 in 2018. Within a one-year increase, the IRR increased significantly to 1.110 (95% CI, 1.102–1.119; $P<0.001$). The ASR per million population increased by 751.7% from 2.05 in 1999 to 17.46 in 2018. Within a one-year increase, the IRR increased significantly to 1.090 (95% CI, 1.082–1.099; $P<0.001$). The AAPC in the ASR during this period was 11.82%, and the trend was statistically significant ($P<0.05$) (Table 8, Fig. 7).

Lymphoid leukemia

The number of newly diagnosed lymphoid leukemia cases increased by 48.5% from 550 in 1999 to 817 in 2018. The AAPC in incidence cases during this period was 2.77%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.028 (95% CI, 1.025–1.031; $P<0.001$). The CIR per million population increased by 36.6% from 11.66 in 1999 to 15.93 in 2018. Within a one-year increase, the IRR increased significantly to 1.024 (95% CI, 1.017–1.030; $P<0.001$). The ASR per million population increased by 33.7% from 11.62 in 1999 to 15.54 in 2018. Within a one-year increase, the IRR increased significantly to 1.022 (95% CI, 1.016–1.029; $P<0.001$). The AAPC in the ASR during this period was 2.21%, and the trend was statistically significant ($P<0.05$) (Table 9, Fig. 8).

Hodgkin lymphoma

The number of newly diagnosed Hodgkin lymphomas increased by 143.1% from 123 in 1999 to 299 in 2018. The AAPC in incidence cases during this period was 4.96%, and the trend was statistically significant. Within a one-year increase, the IRR increased significantly to 1.048 (95% CI, 1.042–1.053; $P<0.001$). The CIR per million population increased by 123.4% from 2.61 in 1999 to 5.83 in 2018. Within a one-year increase, the IRR increased significantly to 1.043 (95% CI, 1.031–1.055; $P<0.001$). The ASR per million population increased by 100.4% from 2.63 in 1999 to 5.27 in 2018. Within a one-year increase, the IRR increased statistically significantly to 1.039 (95% CI, 1.027–1.052; $P<0.001$). The AAPC in the ASR during this period was 4.04%, and the trend was statistically significant ($P<0.05$) (Table 10, Fig. 9).

DISCUSSION

In the ROK, hematologic malignancies have a relatively low proportion of all cancers. None of the hematologic malignancies were among the top 10 types of cancers with the highest incidence in the ROK in 2018. Non-Hodgkin's lymphoma (5,216 cases), leukemia (3,494 cases), and multiple myeloma (1,719 cases) were ranked 11th, 14th, and 20th in the ROK in 2018, respectively [5]. The number of deaths in the ROK from non-Hodgkin lymphoma, leukemia, and multiple myeloma was 2,015, 1,911, and 961, respectively, in 2019, ranking 9th, 10th, and 16th in total cancer deaths, all in respective order [1]. Since the Annual Report of Cancer

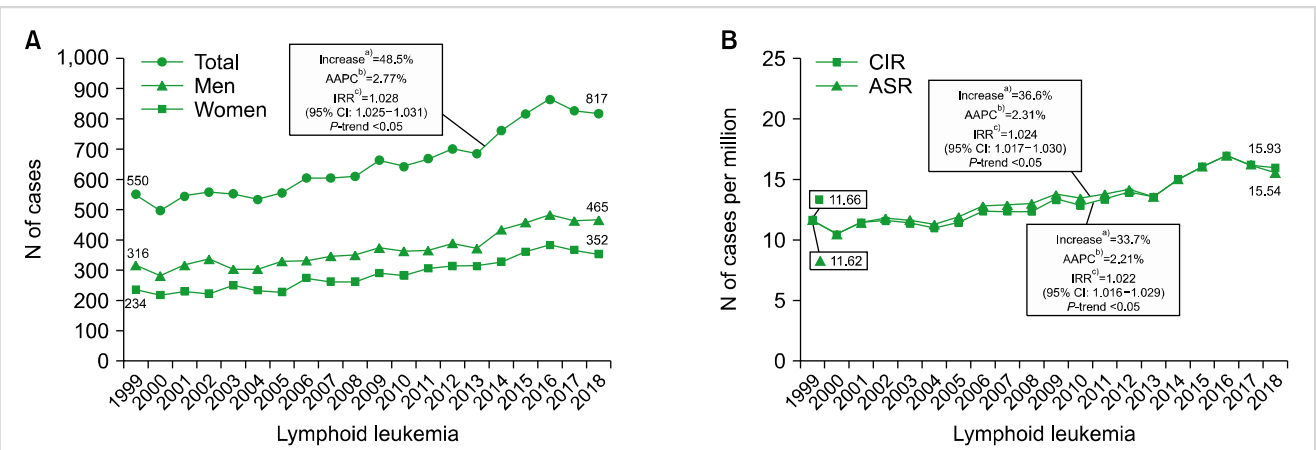

Fig. 8. Annual incidence of lymphoid leukemia in the Republic of Korea. Number of lymphoid leukemia cases **(A)**. Crude and age-standardized incidence rate of lymphoid leukemia per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Table 10. The incidence case number of Hodgkin lymphoma,trend in crude incidence rates, and age-standardized incidence rates per million population in the Republic of Korea from 1999 to 2018.

Years	N of cases				CIR	ASR[a]	ASR[a]	
	Men	Women	Total	AAPC (%)			AAPC (%)	IRR (per yr)
1999	86	37	123	4.96[b]	2.60795	2.63335	4.04[b]	1.039[b]
2000	90	44	134		2.81903	2.81903		
2001	100	48	148		3.09125	3.07055		
2002	83	62	145		3.01294	2.98565		
2003	112	46	158		3.27065	3.22256		
2004	145	59	204		4.20746	4.14143		
2005	105	53	158		3.24548	3.09513		
2006	109	68	177		3.62059	3.47111		
2007	131	74	205		4.17257	3.92396		
2008	131	88	219		4.43278	4.23004		
2009	146	74	220		4.43041	4.16283		
2010	171	77	248		4.97195	4.57967		
2011	168	98	266		5.30817	5.12413		
2012	179	90	269		5.34310	5.02603		
2013	171	93	264		5.22163	4.82687		
2014	170	111	281		5.53551	5.16737		
2015	174	98	272		5.33839	4.95872		
2016	205	110	315		6.16282	5.66606		
2017	172	117	289		5.64115	5.47652		
2018	181	118	299		5.82836	5.27499		

[a]Calculated by defining the 2000 mid-year Korean population (July 1, 2000) as the standard population. [b]Statistically significant trend ($P<0.05$).
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CIR, crude incidence rate; IRR, incidence rate ratio.

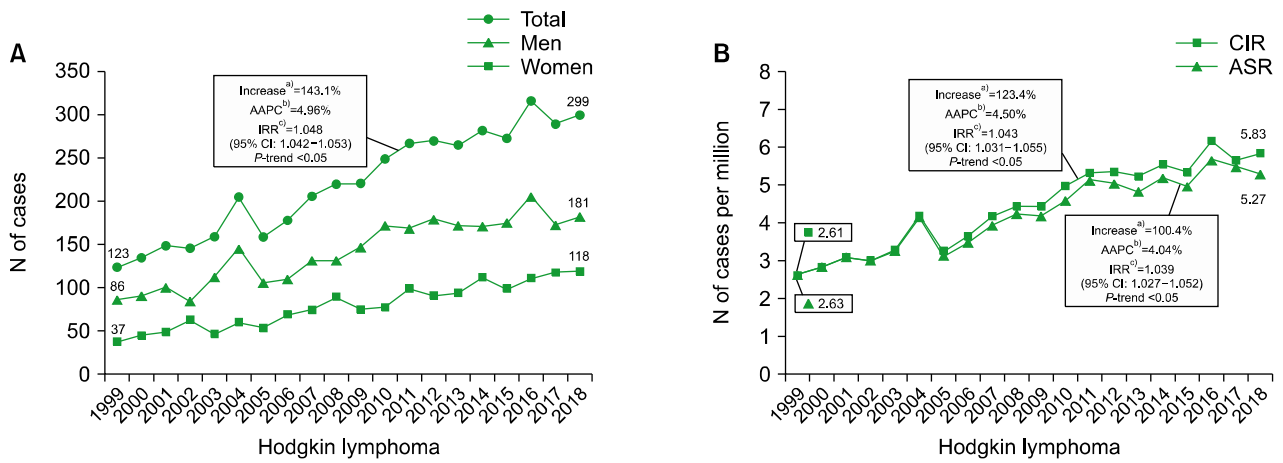

Fig. 9. Annual incidence of Hodgkin lymphoma in the Republic of Korea. Number of Hodgkin lymphoma cases **(A)**. Crude and age-standardized incidence rate of Hodgkin lymphoma per million using the 2000 Korean standard population **(B)**. [a]Comparing 1999 and 2018. [b]Average annual percent change by Joinpoint regression analysis. [c]Incidence rate ratio per year from 1999 to 2018 as calculated by Poisson regression.
Abbreviations: AAPC, average annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CIR, crude incidence rate; IRR, incidence rate ratio.

Statistics mainly describes the most common types of cancer, it is up to each researcher to analyze the statistical data of specific cancers. However, the incidence of hematologic malignancies has been increasing in the ROK. Thus, a more precise and periodic statistical analysis is needed [8]. All hematologic malignancies that were analyzed in this study showed a significant increase in the incidence. The order of increase in ASR over 20 years was as follows: malignant immunoproliferative diseases (AAPC=11.82%, IRR=1.090, $P<0.05$), myeloproliferative disorders (AAPC=9.87%, IRR=1.080,

$P<0.05$), myelodysplastic syndrome (AAPC=7.59%, IRR=1.064, $P<0.05$), Hodgkin lymphoma (AAPC=4.04%, IRR=1.039, $P<0.05$), multiple myeloma (AAPC=3.05%, IRR=1.030, $P<0.05$), non-Hodgkin lymphoma (AAPC=2.26%, IRR=1.023, $P<0.05$), lymphoid leukemia (AAPC=2.21%, IRR=1.022, $P<0.05$), myeloid leukemia (AAPC=1.44%, IRR=1.014, $P<0.05$), and leukemia (AAPC=0.94%, IRR=1.009, $P<0.05$).

Several previous studies on hematologic malignancies in the ROK have shown similar results as obtained in this study. In the analysis from 1999 to 2008, the incidence and the ASR of all hematologic malignancies showed an increasing trend. The latter increased from 10.2% to 13.7%, and the AAPC was 3.9% [9]. Other studies from 1999 to 2012 on myeloid and lymphoid malignancies showed an increasing trend in CIR and overall ASR. The ASR for all myeloid malignancies increased from 3.31 in 1999 to 5.70 in 2012, with an AAPC of 5.4% [10]. In 2012, the ASR per 100,000 persons with 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 increased yearly from 1999 [11]. In a recent study from 2005 to 2015, the incidence and prevalence rates of hematological malignancies increased steadily. From 2005 to 2015, the number of new patients with hematologic malignancies showed an overall gradual increase, with an increase rate of up to 56.7% over 10 years [8]. A similar trend has been observed worldwide. In an analysis of the global burden of disease data from 1990 to 2017, the number of new cases increased [12]. The ASR for all hematologic malignancies increased, except for acute lymphocytic leukemia and chronic myeloid leukemia [13]. Han *et al.* also demonstrated decreased ASR of acute lymphocytic leukemia and chronic myeloid leukemia, but this was not statistically significant, which is similar to the results from previous global research [8, 12, 13]. In this study, the incidence of leukemia was relatively low compared to that of other hematologic malignancies. In addition, in most hematological malignancies, the incidence was higher in males, which is also similar to the results of previous studies [8-15].

There are several possible factors contributing to the increasing trend in the incidence of hematologic malignancies. Age is the most important risk factor for cancer, and the overall incidence of cancer increases with an aging population [16]. Previous studies have also shown that the incidence of hematologic malignancies increases with age [9, 17]. However, it is difficult to explain how the incidence of hematologic malignancies increases because of the aging population alone. In addition to the increase in CIR, ASR also tends to increase significantly. In addition to the aging population, the following possibilities can be considered as possible causes for the increase in hematologic malignancies. First, there is a possibility of a detection bias. Improved access to healthcare facilities and the use of new screening and diagnostic technologies may be another cause [18, 19]. Exposure to diagnostic or therapeutic ionizing radiation, such as X-rays, computed tomography (CT), gamma rays, radiopharmaceuticals, and charged particles can also increase the risk of hematologic malignancies [20, 21]. One study found that the risk of radiation-induced malignancies from CT radiation may increase as CT-based screening becomes more widely used at the population level [22]. The increased exposure to extremely low-frequency electric and magnetic fields (ELF-EMFs) may be another cause [23, 24]. Over the last half century, the use of chemicals has continuously increased, and new chemicals have been developed. The possibility that such exposure to diverse chemical pollution in the workplace or residence may have been a cause of hematologic malignancies cannot be ruled out [25, 26]. Efforts are needed to determine new environmental cancer risk factors in the future.

This study had the following limitations. First, this study used the 61 sets of cancer incidence data provided by the KOSIS. Therefore, hematologic malignancies cannot be analyzed in greater detail. In the future, it will be necessary to analyze hematologic malignancies in a more subdivided manner. Clinically important diseases such as acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, T-cell lymphoma, and B-cell lymphoma require additional detailed analysis. Second, the analysis results of this study may be slightly different from the annual report of cancer statistics. This is due to differences in statistical analysis methods, statistics package programs, and/or standard population settings (Segi's world standard population or Korean standard population) used, along with differences in the handling of decimal places. It would be better to interpret the current state of occurrence based on trends rather than detailed numbers.

An aging society is when the proportion of the population aged $\geq$65 years comprises 7% of the total population, an 'aged society' when it is over 14%, and a 'post-aged society' when it is over 20%. The ROK entered an aging society in 2000, an aged society in 2018, and is expected to enter a post-aged society by 2025. In 2050, the proportion of the population aged $\geq$65 years is expected to be 39.8% [27]. It is highly likely that the incidence of hematologic malignancies will continue to increase with the aging population. In addition to social and medical preparations for the possibility of this increase, more research should be conducted in the future. More well-designed studies are needed to elucidate the causes of this increase.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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