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국내 혈액암 질환의 증가 양상: 2005년부터 2015년까지 국민건강보험 빅데이터에 근거하여

Gradual Increase in Hematologic Malignancy in Korea from 2005 to 2015 Based on the National Health Insurance Service Data

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Background: Hematologic malignancies have a relatively lower prevalence than major solid cancers, although the incidence of hematologic malignancies has significantly increased in recent years. However, understanding the current status of hematologic malignancy is significantly challenging because basic data regarding this malignancy are insufficient in the Korean population.
Methods: From 2005 to 2015, the status of seven codes of hematologic malignancy, containing 24 subcodes defined using a classification defined by the Korean Classification of Disease-6, was analyzed. The number of new patients, crude incidence rate, prevalence rate, and age-standardized incidence rate were also investigated. Results were analyzed based on National Health Insurance Service (NHIS) data.
Results: The number of new patients showed an overall increase over time and a rate of increase up to 56.7% for 10 years. The number of male patients was higher than that of female patients, with the majority of patients aged greater than 60 years. The incidence and prevalence rates have increased steadily.
Conclusions: Consistent with the previous studies, this study might be useful to understand the current status of hematologic malignancy and might contribute to the improvement of national public healthcare.

Key Words: Hematologic malignancy, South Korea, Crude incidence rate, Prevalence rate

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INTRODUCTION

Recently, the incidence of some hematologic malignancies such as lymphoma and multiple myeloma (MM) has been gradually increasing, but hematologic malignancies still comprise a relatively lower proportion of the whole cancer incidence compared to other major solid cancers [1]. However, insufficient basic data exist on hematologic malignancies in Korea.

Several large-scale studies on hematologic malignancies were widely conducted in Korea [2-4]. The first nationwide study was conducted from 1999 to 2008 to analyze the statistics of hematologic malignancy in Korea, provided that significant research data about the overall status of hematologic malignancies were available at that time; however, the study used data from the last 10 to

20 years [2]. Moreover, the studies on myeloid malignancy and lymphoid malignancy, from 1999 to 2012, offered more detailed analysis data compared to the previous study [3, 4].

An Annual Report of Cancer Statistics for 2015 was the latest research data on the incidence of hematologic malignancies in Korea [5]. According to the report, the number of people who have been diagnosed with hematologic malignancies has gradually increased despite the lower incidence proportion of hematologic malignancies in overall cancer [5].

This study aimed to present a diverse range of background information on hematologic malignancy by analyzing longitudinal big data from the National Health Insurance Service (NHIS) from 2005 to 2015 for an improvement in national public healthcare.

MATERIALS AND METHODS

1. Data source and research subjective disease codes

This study presented the claims from the NHIS in Korea from 2003 to 2015. To minimize diagnostic errors, data from 2003 and 2004 were not considered. The main objects were seven codes of hematologic malignancy defined by the Korean Classification of Disease-6 (KCD-6) [6]. During the study, hospitalized individuals designated with the seven codes of hematologic malignancy and one code of other diseases related to hematologic malignancy were included (Table 1). The claims were sorted in chronological order, and the first day of the claim was defined as the first day of diagnosis. Information about sex and age of the patients was obtained. Patients' ages were analyzed in units of 10 years. This study

Table 1. Research subjective disease codes defined by the Korean Classification of Disease-6: hematologic malignancies and diseases related to hematologic malignancies

Major	Disease	Minor	Disease
C90	Multiple myeloma and malignant plasma cell neoplasms	C900	Multiple myeloma
		C901	Plasma cell leukemia
		C902	Extramedullary plasmacytoma
C91	Lymphoid leukemia	C910	Acute lymphoid leukemia
		C911	Chronic lymphocytic leukemia of B-cell type
		C913	Prolymphocytic leukemia of B-cell type
		C914	Hairy cell leukemia
		C915	Adult T-cell lymphoma/leukemia (HTLV-1-associated)
		C917	Other lymphoid leukemia
C92	Myeloid leukemia	C920	Acute myeloblastic leukemia
		C921	Chronic myeloid leukemia, BCR/ABL-positive
		C922	Atypical chronic myeloid leukemia, BCR/ABL-negative
		C923	Myeloid sarcoma
		C924	Acute promyelocytic leukemia
		C925	Acute myelomonocytic leukemia
		C927	Other myeloid leukemia
C93	Monocytic leukemia	C930	Acute monoblastic and monocytic leukemia
		C931	Chronic myelomonocytic leukemia
		C937	Other monocytic leukemia
C94	Other leukemia of specified cell type	C940	Acute erythroid leukemia
		C942	Acute megakaryoblastic leukemia
		C944	Acute panmyelosis with myelofibrosis
C95	Leukemia of unspecified cell type	C950	Acute leukemia of unspecified cell type
C96	Other and unspecified malignant neoplasms of the lymphoid, hematopoietic, and related tissue	C962	Malignant mast cell tumor
D46	Myelodysplastic syndromes	D460	Refractory anemia without ring sideroblasts, so stated
		D461	Refractory anemia with ring sideroblasts
		D462	Refractory anemia with excess of blasts
		D465	Refractory anemia with multi-lineage dysplasia
		D467	Other myelodysplastic syndromes

was approved by the Institutional Review Board of the NHIS Ilsan Hospital (2017-01-001) and Kyung Hee University Hospital (2018-08-027) .

2. Incidence and prevalence analysis

A crude incidence rate (CIR) is defined as the number of new patients in a specified population during a year per 100,000 people. It was calculated using the following formula:

$$\frac{\text{The number of new patients}}{\text{Midyear population}} \times 100{,}000$$

The age-standardized incidence rate (ASR) is defined as the weighted average incidence rate of the age-specific rate. The standard population for the ASR in our study was obtained from the midyear population of Korea in 2000. The annual percentage change (APC) is an indication of the changes in the annual ASRs, indicating the annual increase or decrease rate of cancer incidence rate. The prevalence rate (PR) is defined as the number of patients who have the disease in a specified population during a year per 100,000 people. It was calculated using the following formula:

$$\frac{\text{The number of new and preexisting patients}}{\text{Midyear population}} \times 100{,}000$$

3. Other diseases related to hematologic malignancy

The status of new patients diagnosed with myelodysplastic syndrome (MDS) (D46) among the disease codes related to hematologic malignancy in the KCD-6 (Table 1) was investigated.

4. Statistical analysis

Statistical analysis of big data from the NHIS was performed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute Ind., Cary, NC, USA).

RESULTS

1. Annual new patients' status of hematologic malignancy: C90 to C96

The number of new patients in the study was 52,757, and this

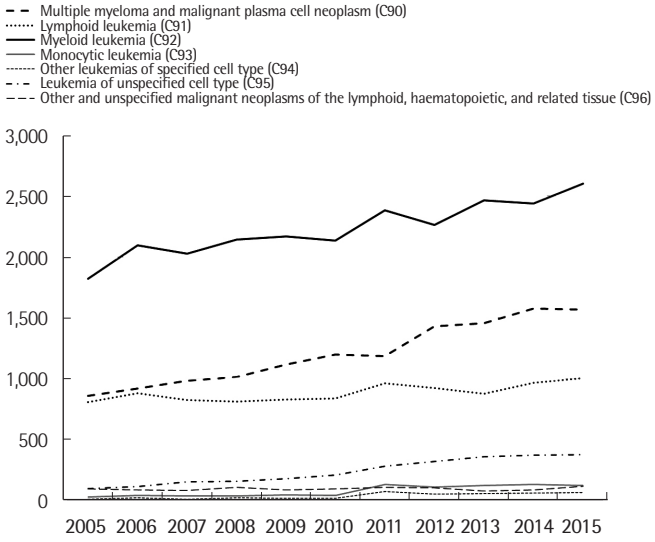

Fig. 1. Number of new patients diagnosed with hematologic malignancies from 2005 to 2015 by the National Health Insurance Service of Korea.

Table 2. Number of new patients diagnosed with hematologic malignancies from 2005 to 2015 by the National Health Insurance Service of Korea according to sex

Code*	Gender	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
C90	Male	456	490	510	538	611	638	649	803	770	850	836	7,151
	Female	408	433	474	479	506	563	540	628	687	726	734	6,178
C91	Male	496	516	474	473	469	487	524	527	485	548	581	5,580
	Female	315	371	350	342	365	353	433	405	394	424	427	4,179
C92	Male	1,013	1,188	1,105	1,183	1,210	1,205	1,345	1,264	1,390	1,390	1,472	13,765
	Female	808	905	922	960	958	926	1,034	998	1,072	1,046	1,127	10,756
C93	Male	17	22	26	25	24	27	83	64	75	75	77	515
	Female	18	26	18	16	27	22	52	50	55	60	51	395
C94	Male	8	16	9	18	18	15	47	37	38	44	42	292
	Female	8	10	5	10	5	7	31	19	25	21	27	168
C95	Male	57	70	90	100	102	107	150	189	184	190	211	1,450
	Female	47	51	70	64	82	108	136	134	181	186	170	1,229
C96	Male	62	51	50	57	44	53	43	59	39	44	46	548
	Female	37	43	36	57	46	48	70	48	44	48	74	551

*See Table 1.

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number gradually increased from 2005 to 2015 (total increase rate, 56.7%; 5,875/3,749) (Fig. 1). In this study, the number of cases of myeloid leukemia (C92) was the highest (46.5%) followed by those of MM and malignant plasma cell neoplasm (C90) (25.3%) and lymphoid leukemia (C91) (18.5%). Regarding sex, the number of males newly diagnosed with hematologic malignancy was higher than that of females in all hematologic malignancy codes except other and unspecified malignant neoplasms of the lymphoid, hematopoietic, and related tissue (C96). Moreover, the highest difference in number was observed in myeloid leukemia (C92) (Table 2). Regarding age distributions, the age group with the largest number of new patients was patients in their 60s (20.0%, 10,542/52,757), followed by patients in their 70s (19.1%, 10,066/52,757). The age group under 9 years constituted the largest proportion in lymphoid leukemia (C91) during the study (22.3%, 2,177/9,759).

2. Crude incidence rate and age-standardized incidence rate

From 2005 to 2011, acute myeloblastic leukemia (C920) showed the highest CIR (up to 2.65), and after 2012, MM (C900) showed the highest CIR (up to 2.89). The CIR of chronic myeloid leukemia, BCR/ABL-positive (C921), ranged from 0.83 (in 2009) to 1.05 (in 2015). Acute lymphoid leukemia (C910) was the code with a CIR of greater than 1 during the study (Table 3). During the study, there were three codes with ASR>1. Among them, the ASR of acute myeloblastic leukemia (C920) decreased from 2.16 in 2005 to 1.97 in 2015, and the APC was -1.88 ($P<0.05$). In chronic myeloid leukemia, BCR/ABL-positive (C921), the ASR remained around 0.7. The ASR of MM (C900) increased from 1.40 in 2005 to 1.65 in 2015, and the APC was 2.17 ($P<0.05$). The ASR of acute lymphoid leukemia (C910) was not statistically significant during the study (Table 4).

3. Prevalence rate

During the study, the PR of all hematologic malignancy codes (C90 to C96) was maintained or increased (Table 5), and the code with the largest PR difference was C900 of MM, which showed an

Table 3. Crude incidence rate in hematologic malignancies by year

Major code*	Minor code*	Year										
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
C90	C900	1.66	1.77	1.84	1.92	2.11	2.19	2.19	2.65	2.7	2.89	2.86
	C901	0.03	0.02	0.02	0.03	0.01	0.03	0.03	0.02	0.02	0.04	0.04
	C902	0.09	0.11	0.14	0.11	0.12	0.18	0.15	0.17	0.15	0.17	0.17
C91	C910	1.27	1.39	1.29	1.23	1.22	1.26	1.25	1.21	1.15	1.24	1.32
	C911	0.31	0.32	0.3	0.3	0.33	0.3	0.38	0.39	0.38	0.45	0.44
	C913	0.01	0.02	0.01	0.03	0.03	0.02	0.06	0.05	0.06	0.05	0.05
	C914	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0	0.01	0.02
	C915	0.01	0.02	0.01	0.01	0.01	0.02	0.02	0.03	0.01	0.03	0.03
	C917	0.06	0.06	0.05	0.06	0.08	0.08	0.19	0.14	0.13	0.13	0.12
C92	C920	2.33	2.58	2.45	2.65	2.74	2.57	2.37	2.25	2.59	2.58	2.63
	C921	0.84	1.02	0.87	0.87	0.83	0.85	0.91	0.87	0.97	0.97	1.05
	C922	0.01	0.01	0.01	0	0	0	0.03	0.05	0.04	0.03	0.03
	C923	0.06	0.04	0.08	0.06	0.05	0.06	0.07	0.05	0.09	0.07	0.08
	C924	0.25	0.28	0.34	0.34	0.36	0.41	0.37	0.37	0.4	0.38	0.45
	C925	0.11	0.16	0.13	0.16	0.15	0.12	0.31	0.25	0.24	0.21	0.25
	C927	0.14	0.2	0.25	0.26	0.23	0.26	0.65	0.62	0.53	0.53	0.6
C93	C930	0.05	0.07	0.07	0.07	0.08	0.07	0.16	0.12	0.11	0.13	0.1
	C931	0.02	0.02	0.02	0.01	0.01	0.03	0.11	0.1	0.14	0.14	0.15
	C937	0	0.01	0.01	0	0.01	0	0	0.01	0	0	0
C94	C940	0.02	0.03	0.01	0.04	0.03	0.02	0.07	0.04	0.07	0.05	0.06
	C942	0.01	0.02	0.01	0.02	0.02	0.02	0.05	0.04	0.03	0.04	0.03
	C944	0	0	0.01	0	0	0	0.03	0.03	0.03	0.04	0.04
C95	C950	0.21	0.25	0.33	0.33	0.37	0.43	0.57	0.64	0.72	0.74	0.75
C96	C962	0.2	0.19	0.18	0.23	0.18	0.2	0.23	0.21	0.16	0.18	0.24

*See Table 1.

Table 4. Age-standardized incidence rate and annual percentage change in hematologic malignancies by year

Major code*	Minor code*	Age-standardized incidence rate											Annual percentage change
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2005-2015
C90	C900	1.40	1.44	1.45	1.47	1.55	1.53	1.47	1.74	1.69	1.75	1.65	2.17†
	C901	0.03	0.01	0.02	0.02	0.01	0.02	0.02	0.02	0.02	0.03	0.03	2.64
	C902	0.08	0.09	0.11	0.09	0.09	0.14	0.10	0.12	0.11	0.11	0.11	3.10†
	C910	1.36	1.50	1.40	1.35	1.35	1.38	1.39	1.35	1.26	1.37	1.48	-0.17
C91	C911	0.27	0.26	0.25	0.23	0.24	0.22	0.26	0.26	0.25	0.28	0.26	0.48
	C913	0.01	0.01	0.01	0.03	0.02	0.02	0.05	0.03	0.05	0.04	0.04	15.81†
	C914	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.05
	C915	0.01	0.02	0.01	0.01	0.01	0.01	0.02	0.03	0.01	0.02	0.02	9.75†
	C917	0.06	0.06	0.05	0.06	0.07	0.07	0.20	0.13	0.12	0.12	0.09	9.50†
C92	C920	2.16	2.38	2.21	2.32	2.35	2.12	1.96	1.85	2.03	1.98	1.97	-1.88†
	C921	0.78	0.92	0.79	0.76	0.71	0.72	0.76	0.71	0.77	0.76	0.84	-0.45
	C922	0.01	0.00	0.01	0.00	0.00	0.00	0.02	0.03	0.02	0.02	0.02	20.20†
	C923	0.06	0.04	0.08	0.06	0.05	0.05	0.06	0.04	0.07	0.06	0.06	1.16
	C924	0.24	0.26	0.31	0.32	0.32	0.37	0.33	0.32	0.35	0.34	0.39	3.47†
	C925	0.11	0.15	0.12	0.14	0.14	0.10	0.26	0.21	0.19	0.17	0.19	5.79†
	C926							0.03	0.02	0.01	0.01	0.01	
	C927	0.13	0.19	0.22	0.22	0.19	0.20	0.53	0.48	0.40	0.38	0.43	12.72†
C93	C930	0.05	0.06	0.06	0.06	0.07	0.06	0.13	0.09	0.09	0.10	0.07	5.98†
	C931	0.02	0.02	0.01	0.01	0.01	0.02	0.08	0.07	0.09	0.08	0.09	26.10†
	C937	0.00	0.01	0.01	0.01	0.01	0.00	0.00	0.01	0.00	0.00	0.00	-12.05
C94	C940	0.02	0.03	0.01	0.04	0.02	0.02	0.06	0.04	0.05	0.03	0.04	11.62†
	C942	0.01	0.03	0.01	0.02	0.02	0.02	0.05	0.03	0.03	0.05	0.02	10.57†
	C944	0.00	0.00	0.01	0.00	0.00	0.00	0.02	0.02	0.02	0.03	0.03	33.41†
C95	C950	0.20	0.24	0.30	0.31	0.34	0.39	0.51	0.54	0.63	0.63	0.62	12.87†
C96	C962	0.19	0.19	0.18	0.23	0.19	0.19	0.23	0.24	0.17	0.20	0.27	1.90

*See Table 1; †P-value < 0.05.

increase by 2.59 times from 4.92 in 2005 to 12.75 in 2015. The codes with a PR greater than 10 were C900 of MM and C921 of chronic myeloid leukemia, BCR/ABL-positive.

4. The current incidence state of myelodysplastic syndrome (D46)

Among the five subcodes of MDS (D46), D467 of other MDS had the highest number of new diagnoses (70.1%, 11,346/16,034) and showed a gradual increase in the study. Regarding sex, except for refractory anemia without ring sideroblasts, so stated (D460), the number of new male patients was higher than that of females in most disease codes (Table 6).

DISCUSSION

In the analysis of the current status of hematologic malignancy from 2005 to 2015, the number of new patients diagnosed with hematologic malignancy, with increased PR, increased for 10 years. According to a previous study in Korea from 1999 to 2008, the number of new patients showed an increase of approximately 69.1% (8,006/4,735) for total hematologic malignancies [2]. In another study from 1999 to 2012 [3], a rate of increase was approximately 42.8% (1,257/880) for AML and approximately 106.9% (813/393, from 2003 to 2012) for MDS. In this context, a continuous reporting system of the current status of hematologic malignancy in Korea should be firmly established, such as the systems in international studies on hematologic malignancy. Moreover, studies should expand their scope including not only some major cancers but also other minor cancers such as hematologic malignancies.

According to sex, the number of new patients diagnosed with C codes was higher in males than in females. Our results with high male proportions were consistent with those of the previous studies in Korea, Europe, and the USA [2, 3, 7, 8]. Regarding age, the

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Table 5. Prevalence rate in hematologic malignancies by year

Major code*	Minor code*	Year										
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
C90	C900	4.92	5.46	6.12	6.6	7.29	7.96	8.43	9.61	10.47	11.6	12.75
	C901	0.07	0.05	0.06	0.1	0.06	0.08	0.08	0.07	0.07	0.14	0.1
	C902	0.38	0.41	0.56	0.57	0.68	0.78	0.87	0.9	0.91	0.96	1.05
C91	C910	5.95	6.84	7.11	7.32	7.58	7.81	7.9	8.13	8.29	8.57	8.94
	C911	0.8	0.95	1.06	1.12	1.23	1.31	1.41	1.58	1.72	1.89	2.11
	C913	0.02	0.03	0.03	0.06	0.06	0.07	0.11	0.11	0.13	0.13	0.15
	C914	0.03	0.04	0.04	0.05	0.06	0.06	0.08	0.08	0.08	0.09	0.1
	C915	0.03	0.05	0.03	0.02	0.03	0.03	0.06	0.07	0.07	0.08	0.09
	C917	0.26	0.35	0.39	0.36	0.39	0.53	0.71	0.64	0.61	0.68	0.71
C92	C920	6.38	7.47	7.81	8.39	8.91	9.08	8.52	8.64	8.93	9.52	9.84
	C921	4.64	5.2	5.7	6.42	6.97	7.52	8.17	8.71	8.95	9.74	10.57
	C922	0.01	0.01	0.02	0.01	0.02	0.01	0.07	0.1	0.11	0.08	0.1
	C923	0.25	0.26	0.32	0.28	0.33	0.37	0.45	0.42	0.41	0.46	0.44
	C924	0.81	1.04	1.25	1.39	1.57	1.72	1.97	2.05	2.16	2.26	2.43
	C925	0.24	0.31	0.3	0.33	0.35	0.29	0.59	0.67	0.7	0.72	0.79
	C927	0.58	0.78	1.05	0.98	1	1.21	2.07	2.01	2.05	2.13	2.3
C93	C930	0.11	0.14	0.14	0.16	0.17	0.16	0.31	0.3	0.32	0.32	0.33
	C931	0.07	0.06	0.04	0.06	0.06	0.07	0.26	0.31	0.37	0.42	0.46
	C937	0.02	0.03	0.02	0.02	0.02	0.03	0.02	0.02	0.03	0.02	0.02
C94	C940	0.05	0.06	0.05	0.07	0.07	0.06	0.13	0.14	0.16	0.16	0.18
	C942	0.05	0.04	0.04	0.05	0.05	0.06	0.1	0.1	0.09	0.11	0.11
	C944	0.01	0.01	0.02	0.02	0.01	0.02	0.12	0.13	0.14	0.15	0.16
C95	C950	0.54	0.72	0.82	0.85	1.04	1.23	1.62	1.72	1.84	2.01	2.24
C96	C962	0.27	0.28	0.3	0.34	0.29	0.3	0.37	0.34	0.31	0.33	0.37

*See Table 1.

Table 6. Number of new patients with D46 according to sex

Code*	Gender	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
D460	Male	108	117	91	114	125	101	132	98	76	69	77	1,108
	Female	203	202	187	215	182	136	192	164	102	112	91	1,786
D461	Male	13	20	9	1	4	13	12	7	9	6	6	100
	Female	11	16	10	10	9	8	14	11	9	7	9	114
D462	Male	61	35	49	54	53	54	71	78	71	93	108	727
	Female	27	15	23	37	38	21	61	32	37	53	52	396
D465	Male							61	36	52	41	52	242
	Female							53	27	37	44	54	215
D467	Male	334	475	442	529	554	659	633	674	718	760	818	6,596
	Female	334	475	442	529	554	659	633	674	718	760	818	6,596

*See Table 1.

number of new patients aged 50 to 69 years was the highest except in lymphoid leukemia (C91), where young children are more likely to be diagnosed with lymphoid leukemia (C91) than adults [2, 9]. Nevertheless, as most of the newly diagnosed patients were elderly people, new patients might increase continuously in the future.

The increasing CIR during the study was similar to that of the previous studies [2, 3, 7, 8], and it is likely that this will continue in the future because of the aging population. Furthermore, the increasing PR is likely to continue due to an increased survival rate [3, 10].

The code of other MDS (D467) had the largest proportion (70.8%) among MDS (D46) in our study. In the previous studies on the incidence of MDS in Japan, 73% of the cases were also

coded as MDS not otherwise specified [11]. MDS is a heterogeneous group of myeloid disease [12], and the classification of the KCD-6 system does not correspond to the World Health Organization (WHO) classification [13], which is one of the possible reasons regarding the mismatch between the diagnosis and claim codes.

Our study has a limitation, that is, we were not able to include the medical records, which are not integrated in the NHIS claims data, of individual patients. However, a systemic nationwide study was possible through coded data, and this can be useful to illustrate the general status of hematologic malignancies in Korea. Additionally, as mentioned above, the classification of the KCD-6 system does not correspond to the WHO classification. Therefore, a more reliable analysis result will be generated and provided when the classification system is revised, considering the WHO classification.

In summary, our study showed the increasing incidence and prevalence of hematologic malignancies including leukemia and MDS. Therefore, further investigation is required. It is also necessary to consider introducing a continuous reporting system in Korea, such as the Surveillance, Epidemiology, and End Results report from the National Cancer Institute in the USA [7] and the HAEMACARE project from the European HAEMACARE Working Group [8]. This nationwide data could contribute in the studies of hematologic malignancies and would be useful in the improvement of national public healthcare.

요 약

배경: 혈액암은 주요 고형암보다 상대적으로 낮은 유병률을 보이나, 최근 그 빈도가 크게 증가하고 있다. 그러나 혈액암에 대한 질환별 기초 데이터가 충분하지 않기 때문에 전체적 국내 현황 파악이 쉽지 않은 상황이다.

방법: 2005년부터 2015년까지 제6차 한국표준질병사인분류에 의해 분류된 24개의 하위코드를 포함하는 7개의 혈액암 관련 코드를 분석하였다. 신규 환자 수, 조발생률, 유병률 및 연령 표준화 발생률도 조사하였다. 결과 분석은 국민건강보험공단의 자료를 기반으로 하여 이루어졌다.

결과: 신규 환자 수는 시간이 지남에 따라 전체적으로 증가했으며 10년간 최대 56.7%의 증가율을 나타내었다. 남성 환자의 수는 여성 환자보다 많았으며, 대부분은 60세 이상이었다. 발병률과 유병률 또한 꾸준히 증가하고 있다.

결론: 이전 연구들과 함께 본 연구가 국내 혈액암의 현 상황을 파악하는 데 도움이 될 수 있으며 국가 공중보건의 개선에 기여할 수 있기를 기대한다.

Conflicts of Interest

None declared.

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