

Epidemiology of Malignant Lymphoma in Japan

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: December 3, 2019

Revised: December 20, 2019

Accepted: December 22, 2019

Published online: April 23, 2020

ABSTRACT

BACKGROUND: Malignant lymphoma (ML) is one of the main malignant neoplasms of hematopoietic organs. In Japan, the number of deaths due to ML is larger than that due to leukemia. Since ML occurs mainly in the elderly, its influences cannot be ignored in Japan, whose society is rapidly aging.

MATERIALS AND METHODS: Data on the crude incidence rates of ML from 1995 to 2015 were obtained from the site of Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan (National estimates of cancer incidence based on cancer registries in Japan, 1975-2015). Data for the numbers of deaths due to ML (ICD10 codes, C81-85) from 1995 to 2016 in 10-year age categories and their age-adjusted mortality rates were obtained from the vital statistics of Japan. The numbers of persons in 10-year age categories in each year were obtained from the census and the vital

statistics of Japan. For the statistical test of the correlation coefficient (Pearson), t-distribution was employed.

RESULTS: The incidence rates in all the age groups significantly increased. For both sexes, the entire crude mortality increased, and about 98% of the deaths from ML were accounted for by non-Hodgkin lymphoma (C82-C85, NHL). As age increased, the crude mortality rates of NHL went up. The crude mortality rates of NHL in the groups 50-59 and 60-69 years of age significantly decreased, but the change in the group 70-79 years of age was not significant. Only the crude mortality rates in the group 80-89 years of age increased significantly. Thus, there was a discrepancy between the incidence and the mortality rates.

DISCUSSION: One of the possible factors that can explain the increase in the crude incidence rates of ML is the progress of diagnostic techniques. It is possible, e.g., that the approval use of positron emission tomography led to an increase in detection of patients with ML. The discrepancy between the increasing incidence rates and the decreasing mortality rates for the groups 50-59 and 60-69 years of age might be explained by the prolongation of the survival period through the use of new medications such as rituximab.

Key words: Epidemiology; Incidence; Japan; Malignant lymphoma; Mortality

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Nishi M. Epidemiology of Malignant Lymphoma in Japan. *Journal of Tumor* 2020; **8(1)**: 551-554 Available from: URL: <http://www.ghrnet.org/index.php/jt/article/view/2845>

INTRODUCTION

Malignant lymphoma (ML) is one of the main malignant neoplasms of hematopoietic organs. In Japan in 2018, though ML accounted for only 3.5% of the total deaths due to malignant neoplasms (12,993/373,584), it accounted for more deaths than leukemia (8,809). Since ML occurs mainly in the elderly, its influences cannot be ignored in Japan, whose society is rapidly aging.

In this article, the changes in the incidence and mortality rates and related matters are described from the viewpoint of descriptive epidemiology.

MATERIALS AND METHODS

Data on the crude incidence rates of ML from 1995 to 2015 were obtained from the site of Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan (National estimates of cancer incidence based on cancer registries in Japan, 1975-2015) (URL: http://gdb.ganjoho.jp/graph_db/index?lang=ja).

In Japan, the ICD10 has been used since 1995. The codes for ML are C81-C85, i.e., C81 (Hodgkin's disease), C82 (Follicular [nodular] non-Hodgkin's lymphoma), C83 (Diffuse non-Hodgkin's lymphoma), C84 (Peripheral and cutaneous T-cell lymphomas) and C85 (Other and unspecified types of non-Hodgkin's lymphoma). Codes from C82 to C85 correspond to non-Hodgkin lymphomas (NHL).

Data on the numbers of death due to ML (C81-C85) from 1995 to 2016 in 10-year age categories and their age-adjusted mortality rates were obtained from the vital statistics of Japan (URL: <https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=7&tclass1=000001053058&tclass2=000001053061&tclass3=000001053065>).

The numbers of persons in 10-year age categories in each of the years were obtained from the census and the vital statistics of Japan (URL: <https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=7&tclass1=000001053058&tclass2=000001053061&tclass3=000001053072>).

For the statistical test of the correlation coefficient (Pearson), t-distribution was employed.

RESULTS

1. Crude incidence rates of ML from 1995 through 2015

The nationwide obligatory registration of malignant neoplasms started in Japan on January 1, 2016. The data for the incidence until 2015 were based on estimation depending on the data of regional cancer registrations. The number of patients who were diagnosed with ML in 1995 was 11,195 (male 6,376, female 4,819), whereas in 2015 it was 30,103 (male 16,419, female 13,684). For both sexes, the crude incidence rates of ML increased (Figure 1). In 1995, that of males was 10.4 (per 100,000) and that of females, 7.5. However, in 2015, that of males was 26.6 and that of females, 21.0.

Figures 2 and 3 show the changes in the crude incidence rates of

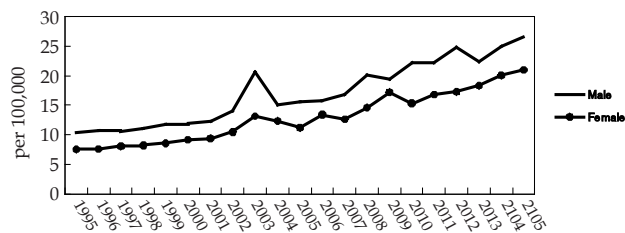


Figure 1 Crude incidence rates of ML.

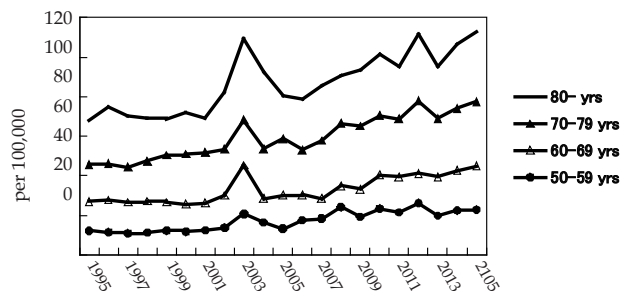


Figure 2 Crude incidence rates of ML (male).

ML in 10-year age categories. Each of the correlation coefficients (vs. calendar year) is shown in Table 1. For both sexes, the incidence rates in all the age groups significantly increased.

2. Crude mortality rates of ML from 1995 through 2016

Table 2 shows the crude mortality rates of each of the ICD codes of ML. Most of the deaths were due to NHL (more than 98%). In all the codes the mortality rates for males were higher than for females by 1.25-1.96-fold.

3. Crude mortality rates of NHL from 1995 through 2016.

Table 3 shows the crude mortality rates of NHL from 1995 to 2016. For both males and females, the crude mortality rates increased. The male/female ratio of the rates was almost constant, ranging from 1.33 to 1.49.

4. Crude mortality rates of NHL in 10-year age categories

For both sexes, as age increased, the crude mortality rates of NHL went up (Table 4).

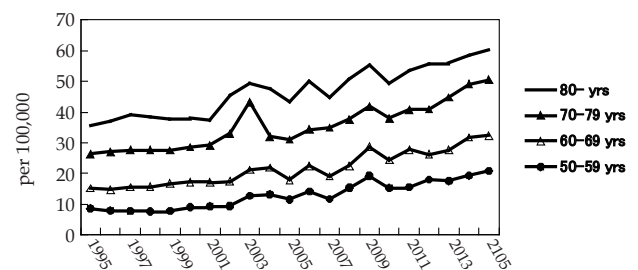


Figure 3 Crude incidence rates of ML (female).

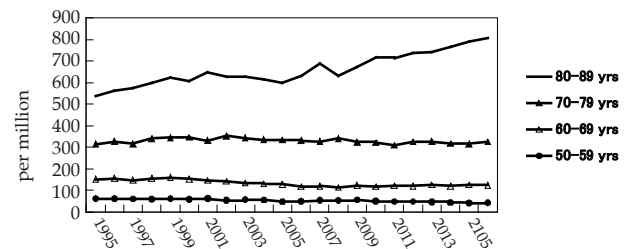


Figure 4 Crude mortality rates of NHL (male).

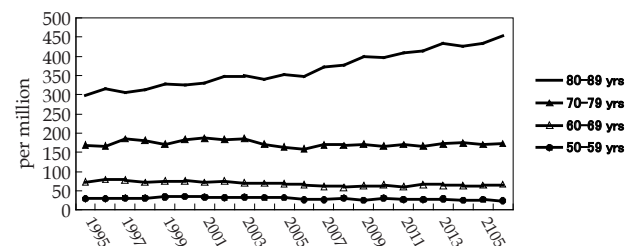


Figure 5 Crude mortality rates of NHL (female).

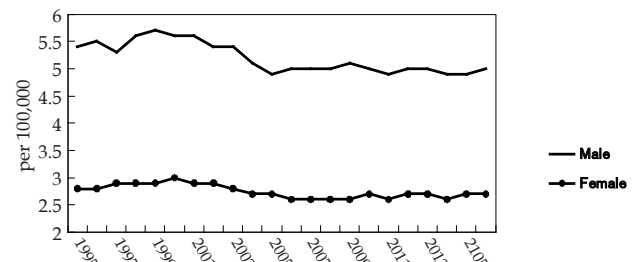


Figure 6 Age-adjusted mortality rates of ML.

5. Changes in the crude mortality rates of NHL in 10-year age categories

Figures 4 and 5 show the changes in the crude mortality rate of NHL in 10-year age categories. Each of the correlation coefficients (vs. calendar year) is shown in Table 1.

For both sexes, the mortality rates in the groups aged 50-59 and 60-69 years significantly decreased, but the change in the group aged 70-79 years was not significant. Only the rates in the group 80-89 years of age significantly increased. Thus, there was discrepancy between the incidence and the mortality rates.

6. Age-adjusted mortality rates of ML

Figure 6 shows the age-adjusted mortality rates of ML. For both sexes, the rates significantly decreased (correlation coefficient: male, -0.822, $p < 0.05$; female, -0.709, $p < 0.05$).

DISCUSSION

The male/female ratio for the mortality rates was more than 1.2 and less than 2.0, irrespective of the age-group or subtype of ML. Several authors have reported the percentage of Hodgkin disease in Japan, which is around 4.0%^[1,2]. In the present study, NHL accounted for the vast majority of the deaths in patients with ML. The crude mortality rate of NHL was, therefore, used for discussion.

According to a report by Yin et al^[3], which employed the data of the Surveillance, Epidemiology, and End Results Program (SEER; 1973-2015), the incidence of extranodal diffuse large B-cell lymphomas (DLBCL) increased steeply from 1996-2003, whereas it decreased during 2003-2015. However, the incidence of ML in Japan has been increasing.

Japanese society is aging. The population aged 65 years or older was 18.26 million in 1995, but in 2015 it was 33.47 million, an about 1.8-fold increase. On the other hand, the increase in the crude incidence rate of ML during the same period was 2.6-fold (26.6/10.4) for males and 2.8-fold (21.0/7.5) for females. The increase in the elderly population may partly account for the increase in the crude incidence rates of ML. A report analyzing 9,426 clinical cases diagnosed from 2007-2014 in Japan showed significant increases in onset age for follicular lymphoma and diffuse large B-cell lymphoma in both men and women^[4].

In addition to the aging of the society, however, there might be some unknown factors that promote the occurrence of ML, though the causes of ML have not clarified yet. One of the possible factors that can explain the increase in incidence is the progress of diagnostic techniques. For example, the use of positron emission tomography (PET) was approved by the Japanese Government in 2003. In that year, the crude incidence rates rose (Figures 1-3). Since the data on incidence were based on estimation, there are errors to some extent. In addition, the data can be affected if there are some large changes in a regional cancer registry. The rise in 2003, therefore, might be due to such artificial causes. It is possible, however, that technical causes such as the approval of the use of insurance for PET led to an increase in the detection of patients with ML in the year of 2003 and thereafter.

Treatment with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen was re-recognized as a standard regimen in a report by Fisher et al^[5], and widely used, but the introduction of rituximab had a large influence on the treatment of ML (CD20 positive B cell lymphoma). Through the use of this medication, the survival rates greatly increased. Yin et al^[3] reported that the five-year survival rates for patients with DLBCL improved dramatically from the 1970s to 2010s (44.15 vs. 63.7%), and they

Table 1 Correlation coefficients (vs calendar year).

Age (years)	Crude incidence rates of ML				Crude mortality rates of ML			
	Male		Female		Male		Female	
50-59	0.880	*	0.944	*	-0.913	*	-0.656	*
60-69	0.796	*	0.938	*	-0.841	*	-0.810	*
70-79	0.926	*	0.906	*	-0.361		-0.348	
80-89	0.838	*	0.944	*	0.938	*	0.980	*

* $P < 0.05$

Table 2 Crude mortality rates of ML from 1995 through 2016 (per million).

Code	C81	C82	C83	C84	C85	C82-85 (NHL)	% of NHL
Total	1.09	0.41	3.01	1.34	66.43	71.19	98.49
Male	1.45	0.45	3.71	1.72	76.94	82.81	98.28
Female	0.74	0.36	2.34	0.98	56.34	60.02	98.78
M/F ratio	1.96	1.25	1.59	1.76	1.37	1.38	

Table 3 Crude mortality rates of C82-C85 (NHL) from 1995 through 2016 (per million).

	Total	Male	Female	M/F ratio
1995	49.97	59.98	40.34	1.49
1996	52.81	63.36	42.68	1.48
1997	54.23	63.45	45.38	1.40
1998	57.18	68.29	46.53	1.47
1999	59.96	71.86	48.16	1.49
2000	61.83	73.22	51.29	1.43
2001	62.98	74.60	51.93	1.44
2002	64.36	75.34	53.85	1.40
2003	66.05	76.94	55.50	1.39
2004	65.54	76.37	55.03	1.39
2005	66.71	76.93	56.75	1.36
2006	67.63	79.36	56.28	1.41
2007	71.63	83.76	59.99	1.40
2008	73.45	85.28	62.26	1.37
2009	77.02	89.36	65.49	1.36
2010	79.62	90.89	68.45	1.33
2011	80.91	92.57	69.62	1.33
2012	84.72	97.46	72.69	1.34
2013	88.37	101.41	76.40	1.33
2014	90.42	103.31	77.60	1.33
2015	93.35	107.40	79.55	1.35
2016	97.13	111.13	83.81	1.33
1995-2016	71.19	82.81	60.02	1.38

Table 4 Crude mortality rates of C82-C85 (NHL) from 1995 through 2016 (per million).

Age (years)	Total	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Total	71.19	0.83	2.03	3.55	5.92	15.56	41.70	99.04	241.83	486.67
Male	82.81	1.10	2.67	4.69	7.49	19.35	53.92	132.37	329.57	683.51
Female	60.02	0.55	1.35	2.36	4.30	11.72	29.64	67.98	172.53	378.58

regarded the introduction of rituximab in the late 1990s as one of the possible reasons. A report by Tan et al^[6] on all the patients with follicular lymphoma treated at Stanford University revealed an improvement in median overall survival from 11 years (1965-1986) to 18.4 years (1987-1996). They estimated that rituximab, approved by the US Food and Drug Administration in 1997, contributed to the improvement. In Japan, the overall crude mortality rate of NHL has increased, but for the groups aged 50-59 and 60-69 years the rates decreased, and that for the group aged 70-79 years was almost constant. Only for the group aged 80-89 years did the rate increase.

This might be partly explained by the prolongation of the survival period. In 2002, rituximab was approved in Japan. Several decades

ago a patient who had NHL at 66 or 67 years of age was likely to die at the age of 68 or 69 years, but now such a patient can live up to age 70 years or more. If such prolongation exists, even when the incidence rate for the group 60-69 years of age increases, the mortality rate for this group decreases. If a similar change occurs in the group aged 70-79 years, then the mortality rate of this group becomes constant, since the inflow from the group 60-69 years of age and the outflow to the group 80-89 years of age balance. Finally, only the mortality rate for the group aged 80-89 years increases.

Thus the contribution of the deaths for the group 80 years of age or older to the increase of the entire crude mortality rate is large. However, the age-adjusted mortality rates have a tendency to decrease. Currently in Japan, the age-adjusted mortality rates are calculated employing the population in 1985 as the standard. In 1985, the population aged 80 years or older was 2.2 million. This is about 22% of that in 2015 (9.9 million). Therefore, the contribution of the crude mortality rate for the group 80 years or older is attenuated when age-adjusted mortality rates are calculated.

At present, several factors are considered to cause ML. Though the eradication of *helicobacter pylori* is effective for gastric mucosa-associated lymphoid tissue lymphoma^[7,8], for most cases of ML no definite factors have been discovered yet and fundamental treatments or prevention cannot be done. Currently, however, several other molecular target drugs such as ibritumomab tiuxetan, ofatumumab, mogamulizumab, and brentuximab vedotin, are used in Japan for malignant lymphoma^[9]. Thus, though its incidence may continue to increase, its crude mortality rate might not increase so much in the near future.

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