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GEOGRAPHIC VARIATION OF HODGKIN'S DISEASE IN JAPAN

HIROYUKI SHIMIZU*[1], KAZUO TAJIMA*[1], TETSUO KUROISHI*[1], SUKETAMI TOMINAGA*[1], and KUNIO AOKI*[2]

*[1] *Division of Epidemiology, Aichi Cancer Center Research Institute*
*[2] *Department of Preventive Medicine, Nagoya University School of Medicine*

ABSTRACT

Death certificates in Japan from 1969 to 1976 were analyzed. Higher mortality rates from Hodgkin's disease were found in the areas along Shibushi Bay, on Yaku Island and on some other small islands of Kagoshima, Nagasaki, and Miyazaki prefectures (range of standardized mortality ratios: 331–2,230). No apparent aggregation of high mortality areas of non-Hodgkin's lymphoma was found although mortality from all malignant lymphomas combined was also generally high in these prefectures in Kyushu. The high mortality from Hodgkin's disease in Kagoshima and Nagasaki prefectures was presumably not due to a bias in clinical diagnosis as far as Japanese autopsy reports (1958–76) were analyzed. It was suggested that etiologic factors for Hodgkin's disease exist which are specific to these prefectures, and especially to some small coastal localities in the southern Kyushu prefectures. (Hodgkin's disease, Japan, Mortality data, Autopsy reports)

INTRODUCTION

The mortality rate of Hodgkin's disease in Japan is low compared to that in other countries.[1] However, several investigators[2~5] have reported a relatively high mortality from Hodgkin's disease in the southwestern parts of Japan. It is conceivable that some clues to the etiology of Hodgkin's disease could be found through examination of the detailed geographic distribution of the disease in these high mortality regions.

The objectives of this study are 1) to examine the geographic distribution of Hodgkin's disease in more detail for Japanese prefectures with a high mortality, 2) to examine the age distribution of Hodgkin's disease in those areas with an especially high mortality, and 3) to examine whether or not the geographic difference of Hodgkin's disease in Japan is due to a bias in clinical diagnosis.

MATERIALS AND METHODS

A copy of the magnetic tape which contains the mortality statistics for malignant lymphomas, including Hodgkin's disease, in Japan during the period from 1969 to 1976, was obtained from the Ministry of Health and Welfare in Japan.

Standardized mortality ratios (SMRs) for Hodkgin's disease (SMR for all Japan = 100) were calculated by sex and five-year age group for each prefecture based on the information from this magnetic tape and from the 1972 census population estimates. Calculation of the

清水弘之・田島和雄・黒石哲生・富永祐民・青木国雄
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SMR for Okinawa prefecture was omitted because mortality data were not available before 1973.

The SMRs for Hodgkin's disease were also computed for each city, town and village in three prefectures with very high SMRs from 1969–1976 by averaging the population estimates, within five-year age groups, between 1970 and 1975. The geographic aggregation of Hodgkin's disease was tested statistically by a method whose validity is proved by the Monte Carlo approach.[6]

The age-specific mortality rates of Hodgkin's disease from 1969–1976 were then calculated by sex and ten-year age group for the Japanese prefectures which showed the highest and lowest SMRs. These age-specific mortality rates were compared to those for all Japan and those for the combined high mortality localities within the high risk prefectures.

In order to examine whether the observed geographic difference in mortality from Hodgkin's disease could be attributable to the variations in methods of clinical diagnosis from one area to another, concordance between clinical and autopsy diagnosis was studied for all autopsied cases of Hodgkin's and non-Hodgkin's lymphomas in both high and low mortality areas. All autopsy cases analyzed here were extracted from *the Annual of the Pathological Autopsy Cases in Japan (vol. 1, 1958 – Vol. 19, 1976)*.[7]

RESULTS

Geographic distribution of Hodgkin's disease within a high mortality prefecture

Fig. 1 shows that in both males and females the SMR for Hodgkin's disease from 1969–1976 was generally high in Kyushu, a major island located in the southwestern part of Japan. The highest SMRs for Hodgkin's disease in Japanese prefectures from 1961–1976 were observed for Kagoshima (239) and Nagasaki (162) prefectures. The SMRs for each city, town and village in Kagoshima and Nagasaki prefectures from 1969–1976 are illustrated in Figs. 2 and 3.

Kagoshima prefecture comprised 14 cities and 82 towns or villages as of 1976. Of these 96 areas, 2 cities and 13 towns or villages showed SMRs (range: 487–2,230) which were at least twice that of the prefecture as a whole. These 15 areas made 9 adjacent pairs and the geographic cluster was statistically significant ($p < 0.05$). Seven of these 15 areas were located at the base of the Osumi Peninsula. Four of these, which form a cluster along Shibushi Bay, showed particularly high SMRs; being 2,230 (11 cases), 2,190 (5 cases), 1,050 (7 cases), and 940 (7 cases). Yaku Island, off the tip of the peninsula, contained two other high mortality areas with SMRs of 1,240 and 1,860.

Nagasaki prefecture comprised 8 cities and 71 towns or villages as of 1976. Of these, four areas showed the SMR (range: 331–1,658) which was at least twice that of the prefecture as a whole. As shown in Fig. 3, one of the four areas was located on a small island at the northern tip of the prefecture (SMR = 1,620) and the other two were located on the Goto Islands (SMR = 1,658 and 635 respectively).

The SMRs for Hodgkin's disease were also examined by city and town for Miyazaki prefecture, since it is geographically adjacent to the areas along Shibushi Bay in Kagoshima prefecture, and since it showed the fourth highest SMR (141) from 1969–1976. In Miyazaki prefecture, four out of 44 areas showed the SMR (range: 306–754) which was at least twice that of the prefecture as a whole. Kushima city, being directly adjacent to the cluster in Kagoshima prefecture, was one of these four high mortality areas (SMR = 596) (Fig. 2).

For comparison with Hodgkin's diseae, Fig. 4 shows the SMRs for all malignant

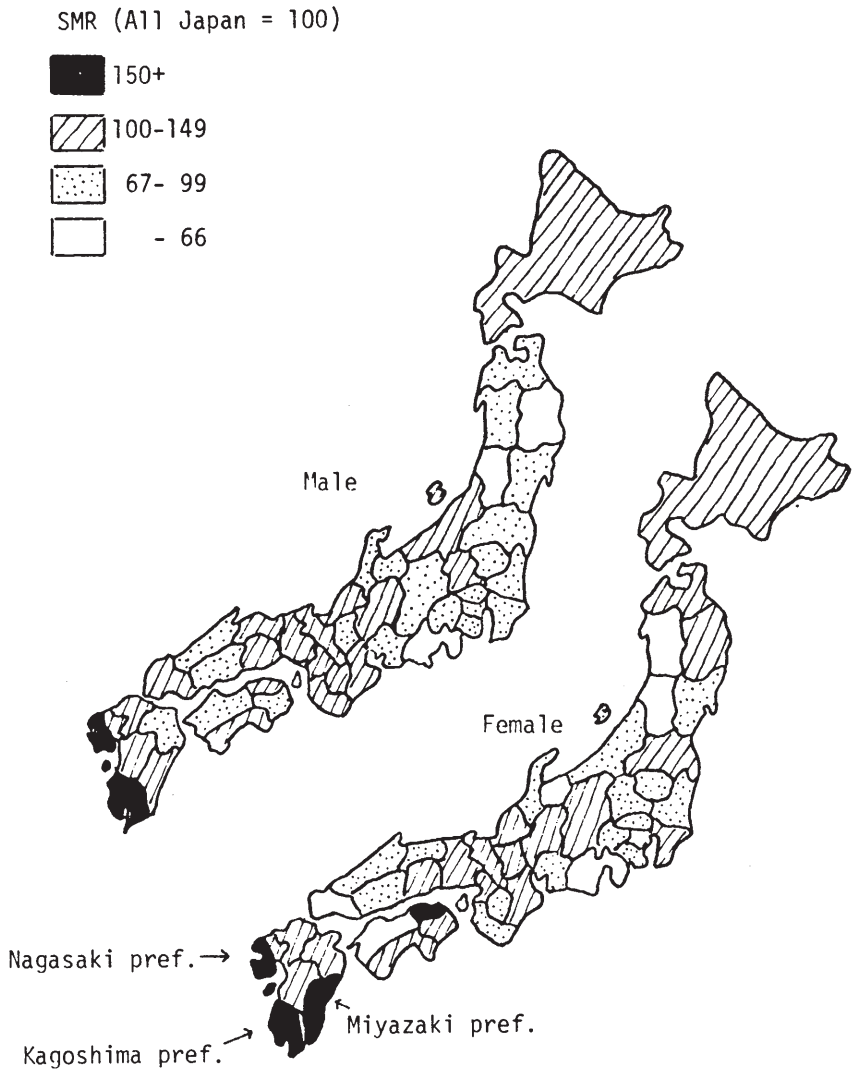

Fig. 1 Geographical comparisons of mortality from Hodgkin's disease† by sex and prefecture in Japan (1969–1976).
† ICD 201 (8th Rev.)

lymphomas combined from 1969–1976 for each city, town and village in Kagoshima prefecture, which had the second highest SMR (204) for all malignant lymphomas during this period. The five localities with high SMRs using the same criteria which we used for the comparison of SMRs of Hodgkin's disease, did not appear aggregated as did the localities with high SMRs of Hodgkin's disease. Similarly, no aggregation of the high mortality areas for all malignant lymphomas was found in Nagasaki prefecture. The ratio of mortality from Hodgkin's disease to that from all malignant lymphomas was about 1:7 in Japan during the study period.

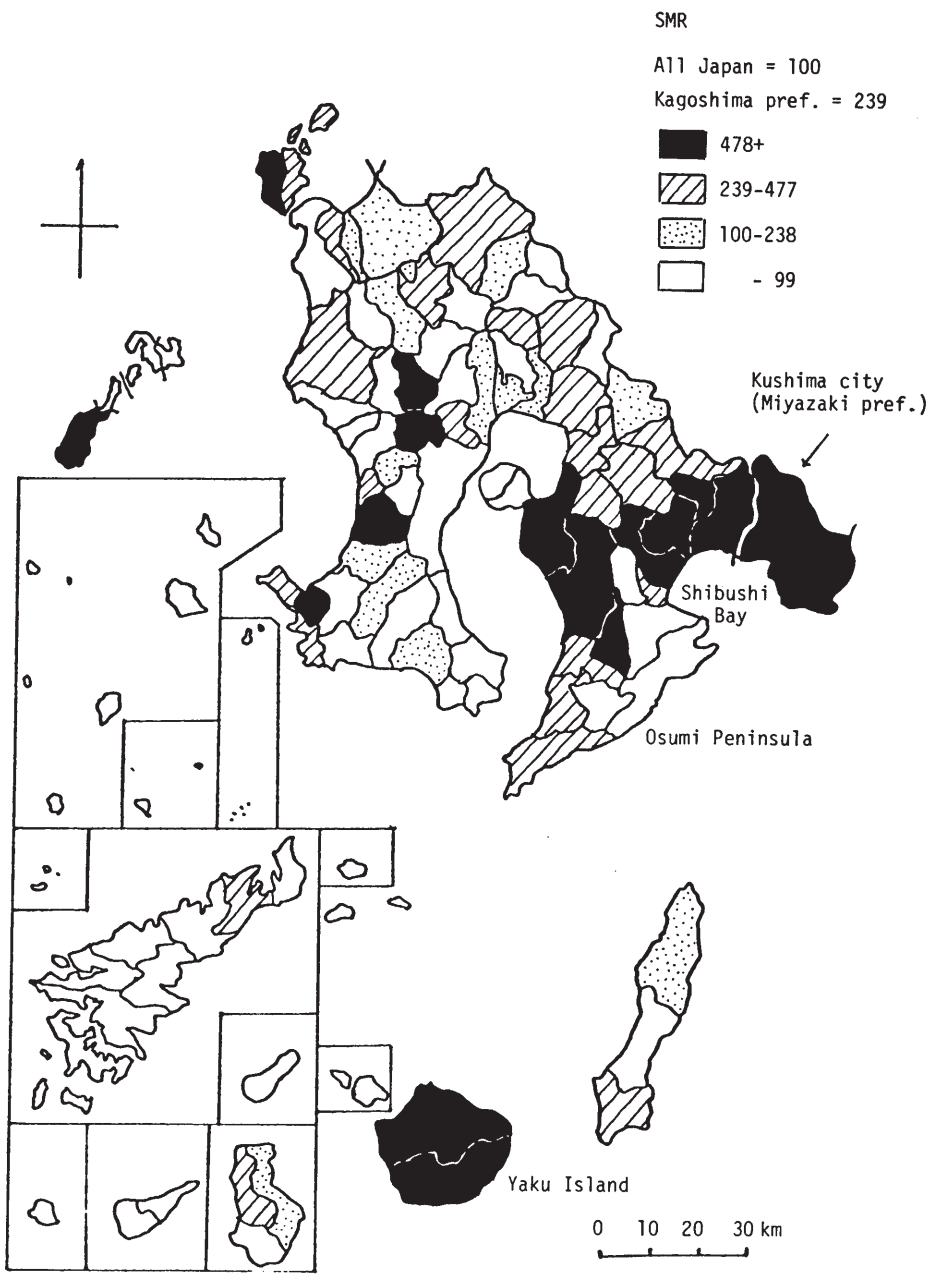

Fig. 2 Geographical comparisons of mortality from Hodgkin's disease† by city and town in Kagoshima prefecture (1969–1976).
† ICD 201 (8th Rev.)

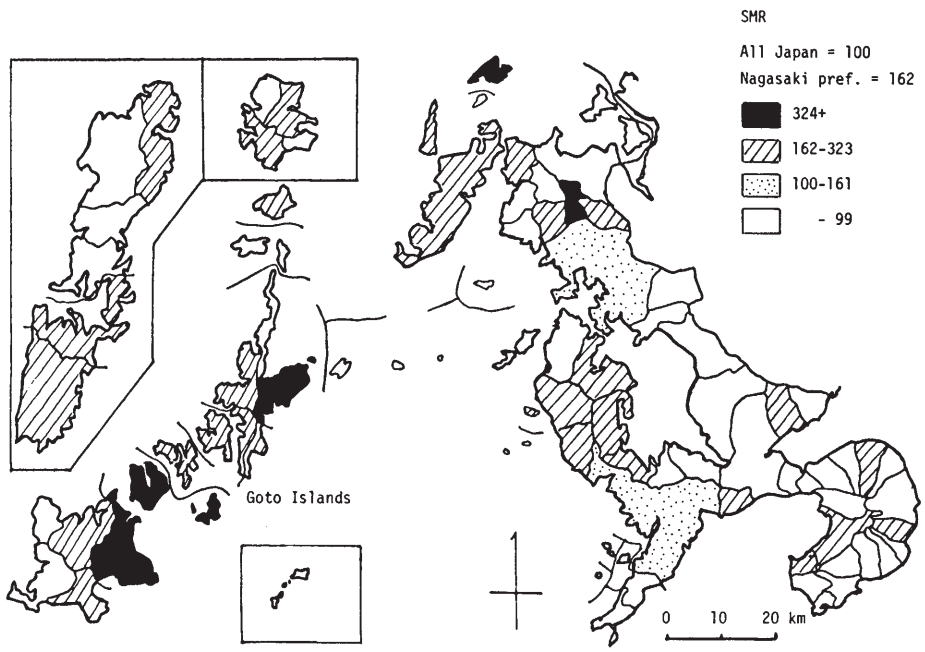

Fig. 3 Geographical comparisons of mortality from Hodgkin's disease† by city and town in Nagasaki prefecture (1969–1976).
† ICD 201 (8th Rev.)

Age-specific mortality rates of Hodgkin's disease in Japan

Fig. 5 shows the age-specific mortality rates for Hodgkin's disease from 1969–1976 for all Japan, for the high mortality areas (Kagoshima and Nagasaki prefectures, 230 cases), for low mortality areas (Shizuoka and Yamagata prefectures, 64 cases), and for the sum of the 21 areas (83 cases) having SMRs of 500 or over in Kagoshima and Nagasaki prefectures. Both men and women aged less than 40 years showed a very low mortality rate from Hodgkin's disease except those in the high mortality localities in Kagoshima and Nagasaki prefectures. A small peak in males aged 20–29 was observed in these high mortality localities although the number of cases in this age group was quite small (3 cases). Age-specific rates for those aged 50 years or over in these high risk localities were also much higher in comparison to those for all Japan.

Validity of clinical diagnosis of the patients with Hodgkin's disease

For validity evaluation, Kagoshima and Nagasaki prefectures were studied as examples of high mortality areas, and four prefectures (Shizuoka, Yamagata, Akita, and Miyagi) were studied as examples of low mortality areas (SMR = 66.5–85.8 in males and 44.9–70.9 in females). From 1958 to 1976, the number of Hodgkin's disease confirmed by autopsy was 94 in the high mortality prefectures and 46 in the low mortality prefectures (Table 1). Of these cases confirmed by autopsy, 40 cases (42.6%) and 35 cases (76.1%) respectively had been diagnosed clinically as Hodgkin's disease in the high and low mortality prefectures. These

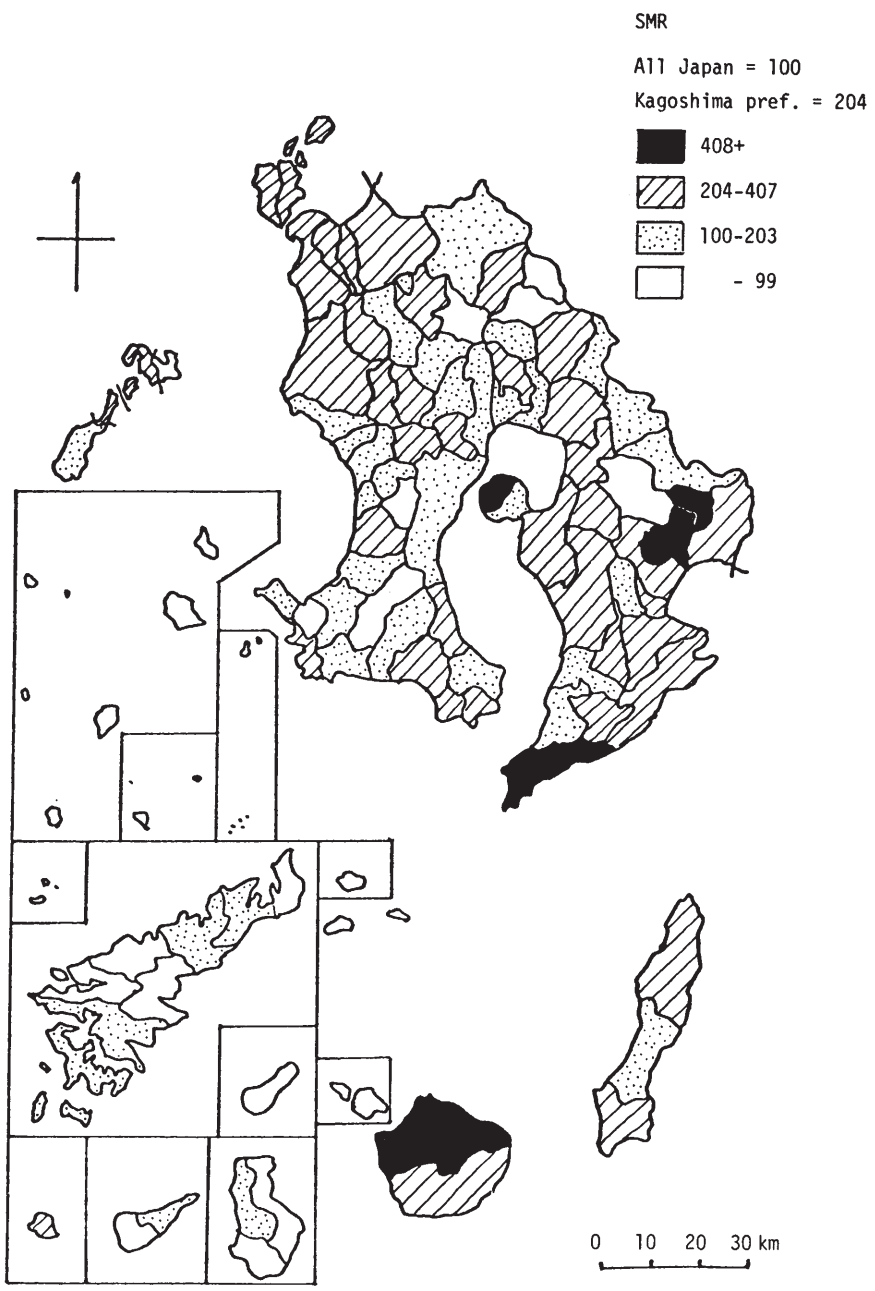

Fig. 4 Geographical comparisons of mortality from all malignant lymphomas† by city and town in Kagoshima prefecture (1969–1976).
† ICD 200–202 (8th Rev.)

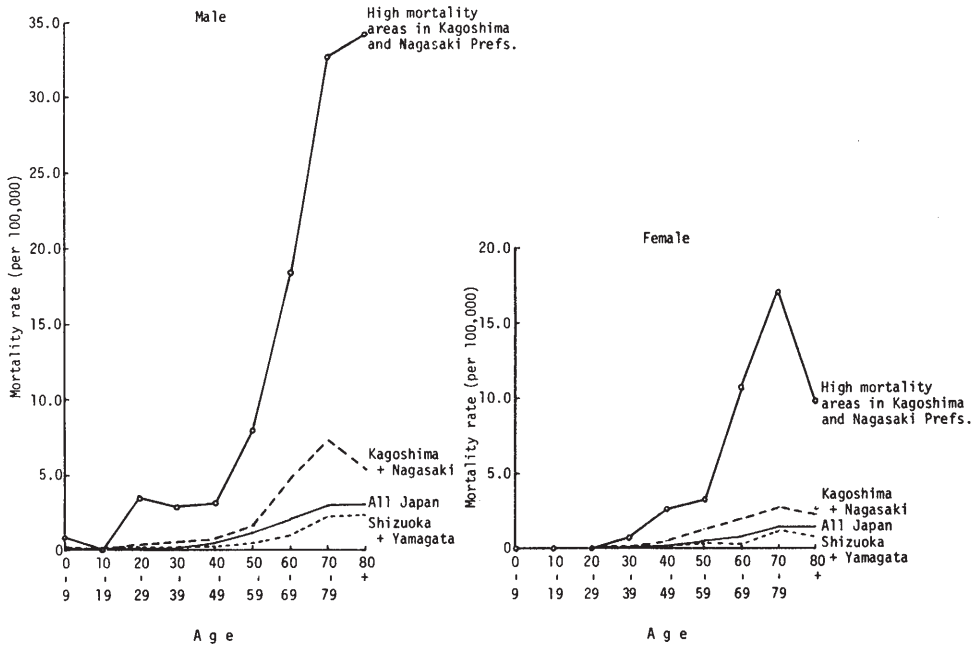

Fig. 5 Age-specific mortality rates of Hodgkni's disease† from 1969–1976 for all Japan, for selected prefectures with high and low mortality and for localities with especially high mortality rates.††

† ICD 201 (8th Rev.)

†† Areas in Kagoshima and Nagasaki prefectures where the SMR was 500 or greater.

percentages are regarded as the sensitivity of the clinical diagnosis. The number of non-Hodgkin's lymphoma confirmed by autopsy in the same period was 547 in the high mortality prefectures and 318 in the low mortality prefectures. Of these, 532 cases (97.3%) and 305 (95.9%) respectivily had been so diagnosed clinically. These percentages are regarded as the specificity of the clinical diagnosis.

Provided that the sensitivity and specificity that prevail in the low mortality prefectures should also prevail in the high mortality prefectures, and provided that autopsy criteria for the diagnosis are the same between low and high mortality prefectures, then 76.1% of the 94 confirmed cases of Hodgkin's disease (72 cases) and (100 − 95.9)% of the 547 confirmed cases of non-Hodgkin's lymphoma (22 cases) in the high mortality prefecure would have been clinically diagnosed as Hodgkin's disease. Instead of 55 clinically diagnosed cases in the group, these would then have been a total of 94. Thus not only does the difference in accuracy of clinical diagnosis fail to explain the difference between the high and low mortality areas, but adjustment for the difference in the sensitivity of clinical diagnosis almost doubles the observed difference.

DISCUSSION

The analysis of autopsy records in this study indicates that geographic difference in Hodgkin's disease in Japan was not due to a bias in clinical diagnosis, since most of autopsied cases may have been diagnosed and treated in major hospitals in each region and since it was

Table 1. Accuracy of the clinical diagnosis of lymphoma† in areas of high and low mortality.

High mortality prefectures (Kagoshima and Nagasaki)

Clinical diagnosis	Autopsy diagnosis		
	Hodgkni's disease	Non-Hodgkin's lymphoma	Total
Hodgkin's disease	40	15	55
Non-Hodgkin's lymphoma	54	532	586
Total	94	547	641
Sensitivity	42.6%		
Specificity		97.3%	

Low mortality prefectures (Shizuoka, Yamagata, Akita, and Miyagi)

Clinical diagnosis	Autopsy diagnosis		
	Hodgkni's disease	Non-Hodgkin's lymphoma	Total
Hodgkin's disease	35	13	48
Non-Hodgkin's lymphoma	11	305	316
Total	46	318	364
Sensitivity	76.1%		
Specificity		95.9%	

† from Annuals of the Pathological Autopsy Cases in Japan (Vol. 1—19)

likely that the clinical diagnosis was based on biopsy findings. The lower sensitivity of clinical diagnosis in Kagoshima and Nagasaki prefectures may suggest that histologic features of the specimens which were diagnosed as Hodgkin's disease in biopsy series were not typical of Hodgkin's disease. Some of these cases may be T-cell lymphoma whose clinico-pathological findings are similar to those of Hodgkin's disease[8] and which are prevalent in rural areas or isolated islands in these prefectures.[9] It appeared that physicians at major hospitals in Kagoshima and Nagasaki prefectures modestly diagnosed cases with malignant lymphoma as Hodgkin's disease by biospy. On the other hand, what we compared in the analysis of autopsy reports may be the comparison between biopsy diagnosis and autopsy diagnosis. Since some cases clinically diagnosed as Hodgkin's disease may not be confirmed by histological examination, then misclassification of the disease entity, from T-cell lymphoma to Hodgkin's disease, might happen in such rural and isolated areas.

We found that villages or towns with a high mortality from Hodgkin's disease were aggregated in the southern part of Kyushu, particularly in the areas along Shibushi Bay. This finding confirms the recent report of Tokunaga *et al.*[10] based on biopsy specimens, who reported the relatively high incidence rate of Hodgkin's disease and other malignant lymphomas in the southeastern part of Kagoshima prefecture. These findings may suggest a common etiologic agent for lymphoreticular malignancies in Kagoshima prefecture in addition to an agent specific to Hodgkin's disease in several local areas of this regions.

One of such etiologic factors may be an environmental agent. Some factors related to agriculture and fishery may be supposed, since these are the major industries in these areas. Schwartz *et al.*[11] observed a cluster of patients with Hodgkin's disease in a small rural town in the USA and postulated the existence of a chronic imuune stimulator such as phytohemagglutinin (PHA), a mitogen which selectively stimulated T-cells. PHA is present in navy beans which constituted a relatively large proportion of the storage capacity of a large grain elevator, the town's only industry.

An infectious agent such as an oncogenic virus may play a role in the etiology of this disease. The peak in the age-specific incidence curve for Hodgkin's disease has been observed for young adults in the United States and some European countries. This has been suspected to consist of those with infectious etiology.[12] In our analysis, howevr, we could not find a clear mortality peak in young adults even in the very high mortality localities in Kagoshima and Nagasaki prefectures.

From historical, sociological and linguistic viewpoints, the ancestors of the residents in the southern Kyushu are considered genetically distinct from those in the northern parts of Japan. Their life styles are also different. Interestingly, a high incidence of Hodgkin's disease and other lymphomas has also been reported in Okinawa (Ryukyu Islands),[13] located about 600 kilometers to the southwest. Aggregation of Hodgkin's disease in local areas of southern Kyushu, particularly in the small isolated islands, might be partly attributed to a high frequency of consanguineous marriages. A cluster of Hodgkin's disease has been reported in a large inbred family in Newfoundland, Canada.[14]

The relationship between immunodeficiency and Hodgkin's disease and other lymphomas is well known.[15~17] Recently Dworsky *et al.*[18] reported a decreased response to mitogen stimulation in healthy members of families with multiple cases of lymphoma when compared to healthy members of families with other forms of cancer. Studies on genetic factors focusing on the immue system of persons born in Kyushu and Okinawa might give a clue to the etiology of both Hodgkin's disease and non-Hodgkin's lymphoma.

In order to further confirm geographic variation of Hodgkin's disease in Japan the study of effects of a bias by variation of pathologic criteria will be also necessary.

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