ORIGINAL CONTRIBUTION

Cancer Mortality in Minamata Disease Patients Exposed to Methylmercury Through Fish Diet

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We report here a historical cohort study on cancer mortality among Minamata disease (MD) patients (n=1,351) in Kagoshima and Kumamoto Prefectures of Japan. Taking into account their living area, sex, age and fish eating habits, the residents (n=5,667; 40 years of age or over at 1966) living in coastal areas of Kagoshima, who consumed fish daily, were selected as a reference group from the six-prefecture cohort study conducted by Hirayama et al. The observation periods of the MD patients and of the reference group were from 1973 to 1984 and from 1970 to 1981, respectively. Survival analysis using the Poisson regression model was applied for comparison of mortality between the MD patients and the reference group. No excess of relative risk (RR) adjusted for attained age, sex and follow-up period was observed for mortality from all causes, all cancers, and non-cancers combined. Analysis of site-specific cancers showed a statistically significant decrease in mortality from stomach cancer among MD patients (RR, 0.49; 95 % confidence interval, 0.26-0.94). In addition, a statistically significant eight-fold excess risk, based on 5 observed deaths, was noted for mortality from leukemia (RR, 8.35; 95 % confidence interval, 1.61-43.3). It is, however, unlikely for these observed risks to be derived from methylmercury exposure only. Further studies are needed to understand the mechanisms involved in the observed risks among MD patients. *J Epidemiol*, 1996 ; 6 : 134-138.

methylmercury, cancer, mortality, leukemia

Minamata disease outbreak occurred in 1953 among fishermen and their families living around Minamata Bay ¹⁾. The disease has been ascribed to high consumption of fish and shellfish contaminated by methylmercury ^{2,3)}. To date, more than 2,000 persons have been officially certified to have Minamata disease (MD), and over 700 of these have died ⁴⁾.

It is well known that mercury accumulates in tissues, especially in human kidney and liver ⁵⁾. Previous epidemiologic studies of MD patients indicated a significant increase of standardized mortality ratio (SMR) for liver disease and renal disease ⁶⁻⁸⁾. In these studies, cause-specific death rates from the general population from surrounding of methylmercury polluted areas were used.

On the other hand, a pathological study showed a high proportion of thyroid and prostate cancers among autopsy cases in the methylmercury polluted areas. ⁹⁾ Experimental studies revealed that methylmercury chloride was carcinogenic to the kidney in mice, but only in male mice ^{10,11)}. However, few epidemiologic data are available to support an association between methylmercury exposure and cancer. To evaluate cancer mortality among MD patients, we compared cause-specific mortality between MD patients in Kagoshima and Kumamoto Prefectures and residents consuming fish daily in coastal regions of Kagoshima Prefecture, a sub-sample of the six-prefecture cohort ¹²⁾.

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MATERIALS AND METHODS

1) Profile of Subjects

From 1970 to 1994, 2,256 inhabitants who met the criteria for diagnosis of Minamata disease established by a government committee, had been medically confirmed to have Minamata disease in Kumamoto and Kagoshima Prefectures. A more detailed description of the diagnostic criteria is available elsewhere ¹³⁾. Cases identified after death were excluded from the subjects, because the difference in case finding method can cause a bias. Previous study emphasized that a few years would be necessary to register the MD patients in Kumamoto and Kagoshima Prefectures after enactment of the Public Nuisance Relief law in 1970 ⁸⁾. Therefore the observation period was from 1973 to 1984 for comparison in this study. Finally, a total of 1,351 MD patients born before 1926 (40 years of age or over at 1966) were used for analysis (Table 1).

A brief description of the six-prefecture cohort study is as follows: A cohort of 265,000 residents, aged 40 or over, from 29 public health districts in six prefectures (Miyagi, Aichi, Osaka, Hyogo, Okayama, and Kagoshima) were surveyed as Hirayama cohort in 1965, and were followed up until 1981 ¹⁴⁾. A one-page questionnaire used in the baseline survey included questions about occupation, smoking, drinking, dietary habits and so on. A total of 41,000 residents in Kagoshima Prefecture were included. At the beginning of each follow-up year, a migration survey was conducted through reference to the local residence registration. The age and sex distribution of the cohort have been reported elsewhere ¹⁵⁾. The Hirayama

cohort covered the five public health districts (Hayato, Kaseda, Nishinoomote, Ohkuchi and Shibushi) in Kagoshima Prefecture. Residents in Ohkuchi were excluded in the present study, because Ohkuchi is located deep inland (mainly in agricultural land) of the Prefecture, whereas the other four districts are coastal (Fig. 1). Based on the questionnaire data, 5,667 residents engaged in fishery and agriculture who reported to consume fish daily were selected as a reference group (Table 1). In this group, the period of 1970 to 1981 was used for the comparison to link the follow-up period of the MD patients. The bias introduced by the difference of calendar years in follow-up is considered to be negligible.

2) Ascertainment of Death

Death information for MD patients was collected at the District Legal Affairs Bureau office in Kumamoto and Kagoshima Prefectures. Causes of death recorded on death certificates are coded according to the 9th revision of the International Classification of Diseases and Injuries (ICD), and the selection of underlying causes of death is based on the WHO rules ¹⁶⁾. This selection is carried out by an experienced nosologist who was blinded regarding the history of methylmercury exposure.

The deaths among the reference group were annually ascertained by checking against death certificates kept at each public health center ¹⁵⁾. Causes of death were coded by T. Hirayama, using the 7th revision of the ICD ¹⁵⁾. Thus, the two kinds of ICD revision were used in the present study, but a comparison was made to take into account revision difference.

Figure 1. Map of study areas.

3) Statistical Procedure

The person-years and the numbers of deaths were aggregated and stratified by sex, attained age (5 year category) and follow-up period (0-6 years, ≥ 7 years) using DATAB computer program¹⁷⁾. Thereafter, survival analysis with Poisson regression model was made by AMFIT regression program¹⁷⁾. The relative risk (RR) and its 95 % confidence interval (CI) were also estimated by the method of maximum likelihood. A more detailed description of the statistical methods is available elsewhere^{18,19)}.

RESULTS

Table 1 shows the number of the deaths by group and cause. There was a total of 338 deaths including 66 cancer deaths among MD patients from 1973 to 1984. Among the reference group, there was a total of 933 deaths including 247 cancer deaths from 1970 to 1981.

Table 2 shows the results based on the reference group (the four subgroups combined). Mortality from all causes, all cancers, and none-cancers combined was not significant difference between the MD patients and the reference group, respectively. Results were essentially not changed when separate analysis

was made for males and females (data not shown).

Table 3 shows the results by site-specific analysis that was made for the sites with five or more deaths among the MD patients. Note here that the RR and its 95 % CI were also calculated based on the reference group (the four subgroups combined). Among MD patients, the cancer sites for which five or more deaths were observed were stomach (13 cases), lung (10 cases), liver (9 cases), and leukemia (5 cases) in this study. Thyroid and kidney cancers were not observed among MD patients, which were toxicologically emphasized by pathological or experimental studies. As shown in the Table 3, significantly lower RR (0.49; 95% CI: 0.26-0.94) was observed for stomach cancer, and significantly higher RR (8.35; 95% CI: 1.6-43.3) was observed for leukemia. It is possible that the separate analysis is made for males and females, adjusting for attained age and follow-up period. The RR for stomach cancer among males was 0.62 with 95% CI of 0.31 to 1.21. Mortality from stomach cancer was not observed among female MD patients. On the other hand, the RRs (95% CI) for leukemia in males and females were 8.45 (0.87-81.31) and 8.24 (0.74-90.82), respectively. These RRs were not statistically significant, although those were similar to the RRs adjusted for sex, attained age and follow-up period. Dose-response relation-

Table1. Number of subjects by sex and number of deaths by cause.

Group	No. of subjects		No. of deaths	
	Male	Female	All causes	All cancers
MD patients	746	605	338	66
Reference group (subgroup)*	2237	3430	933	247
(Kaseda)	835	1614	429	120
(Hayato)	668	929	265	72
(Nishinoomote)	481	542	136	30
(Shibushi)	253	345	103	25

* Subcohort of the six-prefecture cohort member in Kagoshima Prefecture

Table2. Relative risk and its 95% confidence interval by death cause.

Cause of deaths (9th ICD rubrics)	No. of deaths		RR*	95%CI
	MD patients	Reference group		
All causes	338	933	0.94	0.82-1.07
All cancers (140-208)	66	247	0.76	0.57-1.01
Non-cancers (excluded 140-208)	272	686	1.00	0.86-1.16

Relative risk (RR) and 95% confidence interval (95% CI), based on the reference group.

* Adjusted for attained age, sex and follow-up period.

Table3. Site-specific analysis of cancer mortality risk.

Cancer sites (9th ICD rubrics)	No. of deaths		RR*	95%CI
	MD patients	Reference group		
Stomach (151)	13	65	0.49	0.26-0.94
Liver (155)	9	31	0.82	0.37-1.80
Lung (162)	10	42	0.70	0.34-1.45
Leukemia (204-208)	5	2	8.35	1.61-43.30

Relative risk (RR) and 95% confidence interval (95% CI), based on the reference group.

* Adjusted for attained age, sex and follow-up period.

ships could not be determined for stomach cancer or leukemia, because no individual dose on methylmercury exposure was available among the MD patients and the reference group.

With regard to other cancer sites (included in the sites not shown in the table), there were no statistically significant differences in mortality rates between the MD patients and the reference group.

DISCUSSION

In previous studies, the SMRs were calculated using the cause-specific death rates from the local population around the methylmercury-polluted areas⁶⁻⁸. However, these studies did not take into account of fish eating habits. In this study, the reference group was selected from the Hirayama cohort taking into account their area, age, sex and fish eating habits. It is best if the reference group could be selected from the residential areas of MD patients, e.g., Minamata City or Izumi City. Therefore the reference group in this study is second best with regard to geographical control selection. But this study is important in which the cancer mortality of MD patients was compared with that of the local population, adjusting for dietary habits.

Occupational information among the reference group was obtained from the survey at the baseline in the Hirayama cohort in 1965. However, we could not separate farmers from fishermen, because these two occupations were combined in the survey¹⁵. We also could not adjust the quantity of fish consumption because the amount of fish intake per day was not obtained from either MD patients or reference group. Therefore this quantitative difference of fish intake may cause a selection bias, because the MD patients could take a large amount of fish contaminated with methylmercury¹⁻³.

Death certificates for MD patients were collected from the Legal Affairs Bureau office based on legal address (honseki). On the other hand, death certificates for reference group were collected from public health centers based on the present address. However, there were not large differences for follow-up rates (over 90 %) between the MD patients and the reference group. No statistical difference between the MD patients and the reference group was also observed for non-cancers combined that covered about 80 % of mortality from all causes (Table 2). These suggest that the difference in address for death identification was not likely to bias the comparison very much.

Determination of the underlying causes of death for cancer is probably more accurate than for other causes of death based on death certificate. It is also considered that the quality of the death certificate did not significantly differ by study area. Consequently, selection of primary site of cancer is considered to be comparable between the MD patients and the reference group.

Nationwide analysis of mortality by SMR indicated that the lower SMR for stomach cancer was observed in Kumamoto and Kagoshima Prefectures²⁰. Thus the lower RR for stomach cancer in this study could not be explained by area difference (Table 3). However it is biologically difficult to explain the association between stomach cancer and methylmercury exposure. Previous epidemiologic studies showed the nonsignificant SMR for stomach cancer based on the comparison between the MD patients and the local population^{7,8}. Further mortality studies from the follow-up of the MD patients are necessary to confirm those findings.

In Japan, adult T-cell leukemia/lymphoma (ATL) is clustered in Kyushu²¹. Unfortunately there were not sufficient information from MD patients carrying antibody to human T-cell leukemia virus type I (HTLV-I) antigens. Even in Kyushu, ATL was not well recognized in the local hospitals, because ATL virus was identified in 1981²². Recently, the result from the health screening for adults aged 40 or over indicated that about 20 % of local population carried the antibody to HTLV-I antigens in a town, which was located in the methylmercury polluted areas²³. At least, the rate of HTLV-I carriers among the blood donors in adults was about 12 % or below in Kyushu²⁴. Thus, future research for the prevalence of HTLV-I carriers will be necessary to examine whether area difference between the methylmercury polluted areas and the other areas exists or not.

In conclusion, mortality rates were compared between the MD patients and the reference group who consumed fish daily. The present results revealed no excess of RR for mortality from all causes, all cancers, and non-cancers combined. On the other hand, statistically significant RRs were observed for stomach cancer (RR, 0.49) and for leukemia (RR, 8.35), although it is biologically difficult to explain by methylmercury exposure only. Further studies are needed to clarify the observed risks here not only in terms of mortality but incidence to keep away from a limitation of death certificates.

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