

# Mortality among Yusho patients: 40 Years of Follow-Up

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## INTRODUCTION

In 1968, a mass accidental exposure to dioxin-like compounds occurred in western Japan through the ingestion of a contaminated commercial brand of rice oil. Patients suffered a range of symptoms including: acneiform eruptions; pigmentation of the skin, nails and conjunctivas; increased discharge from the eyes; and numbness of the limbs. As of 31 December 2007, 1,918 patients were officially registered as “Yusho”. Since the Yusho incident investigations into PCBs have become more common. Preliminary and interim reports related to mortality among Yusho patients showed that the standardized mortality ratios (SMRs) for liver cancer were significantly increased in males compared with the general population in Japan [1]. It was not clear evidence, because of shortage of observation periods and of diseased cases. Thus, several uncertainties remain regarding the effects of PCBs and PCDFs on mortality. In the present paper based on 40-year follow-up for the Yusho cases, we have re-evaluated the effect of PCBs and PCDFs on major causes of death.

## METHODS

Yusho cases were identified by name, date of birth, sex, address and date and place of registration. Follow-up surveys of vital status were conducted with the cooperation of the municipal hall where the registered patients had lived or were still living. The underlying causes of death identified in the survey were detected by record linkage, matching the follow-up data with the national vital statistics. This information was provided with special permission by the Statistics Bureau of the Ministry of Internal Affairs and Communications (MIAC) of Japan (Bulletin No. 65, Government Gazette, 4769, 18 February 2008).

The record linkage was completed by merging the two data sets according to the match-key variables, which were date of birth, date of death, sex and place of death. Names were not included in the match-key variables because they were not contained in the national vital statistics data provided by the MIAC. However, it has been shown previously that this matching method is a reliable and valid way of tracing a target person. The cases with fully-matched variables from both data sets were retrieved. The day and place of death obtained from the registered data for some of the cases differed from the national vital data. Therefore, we treated patients as fully matched if they matched either on day of death or place of death and had other matched variables. Follow-up rate was 93.0%.

SMRs were calculated according to sex and cause of death by dividing the number of observed deaths by the number of expected deaths in each calendar period. The 95% confidence interval (CI) was calculated for each SMR, assuming that the number of observed deaths was a Poisson distribution and that the expected value was known without error.

## RESULTS

Follow up status for registered Yusho patients are shown in Table 1. Observed and expected numbers of deaths, standardized mortality ratios (SMRs), and 95% confidence intervals for major causes of death among Yusho patients between 1968 and 2007 are shown in Tables 2. The SMR for liver cancer was slightly elevated in both males and females: 1.67 (95% CI: 0.99–2.63) and 1.87 (95% CI: 0.81–3.69), respectively. Among males, the SMR for all-cancer and lung cancer was significantly above expectation compared with the general population: 1.26 (95% CI: 1.03–1.53) and 1.56 (95% CI: 1.03–2.27), respectively.

## DISCUSSION

In this study, we found elevated mortality from all-cancer and lung cancer among males in Yusho patients in comparison with the general population. The results were informative because of the increasing power of the study since follow-up is being continued.

Liver cancer mortality was statistically borderline significant increase among males with a SMR of 1.67 (95% CI: 0.99–2.63). For liver cancer, determination of the hepatic carcinogenicity of these compounds should take into account their concentration in the body, the biological responses to the compounds, and concurrent hepatitis virus infection. According to a report from the Japanese Red Cross, the rates of hepatitis B virus infection (HBs antigen) in each age group throughout Japan did not differ according to region. On the other hand, the rates of hepatitis C infection (HCV) were two- to three-fold higher in the southern region of Japan, especially for those aged 50 years and over [2]. Thus, the elevated risk of liver cancer among Yusho patients [1] could have been due to the geographical differences in hepatitis C virus infection in Japan.

Lung cancer mortality also was elevated among males in the whole period. Several independent studies examining male cohorts with biologically documented exposure to high levels of dioxin found elevated lung cancer risks [3]. The lung cancer is one of the target organs of the carcinogenic action in animals [4]. We did not have individual data on smoking habits, however, the known homogeneity of educational and cultural features between the Yusho patients and general population makes systematic differences quite improbable. Other indirect evidence is provided by the finding that other smoking-related cancers were not elevated.

In conclusion, we have updated the follow-up data and have re-evaluated the effect of PCBs and PCDFs on major causes of mortality. The 40-year follow-up data demonstrates that the mortality risks due to all-cancer and lung cancer among males were significantly increased in comparison with the general population. However, the interpretation is unclear about the carcinogenic effects due to dioxin-like compounds exposure. In Yusho cases, further follow-up study should be unavoidable to clarify the carcinogenic effects.

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## TABLES

**TABLE 1. Number of Yusho patients between 1968 and 2007.**

| Calendar period | Newly registered cases |         |       |
|-----------------|------------------------|---------|-------|
|                 | Males                  | Females | Total |
| 1968–1972       | 566                    | 559     | 1,125 |
| 1973–1977       | 294                    | 245     | 539   |
| 1978–1982       | 53                     | 71      | 124   |
| 1983–1987       | 34                     | 34      | 68    |
| 1988–1992       | 10                     | 3       | 13    |
| 1993–1997       | 2                      | 0       | 2     |
| 1998–2002       | 2                      | 0       | 2     |
| 2003–2007       | 16                     | 29      | 45    |
| Total           | 977                    | 941     | 1,918 |

**TABLE 2. Observed and expected number of deaths, standardized mortality ratios (SMRs), and 95% confidence intervals for selected causes of death among Yusho patients between 1968 and 2007.**

| Cause of death  | Male |       |      |        |      | Female |       |      |        |      |
|-----------------|------|-------|------|--------|------|--------|-------|------|--------|------|
|                 | Obs  | Exp   | SMR  | 95% CI |      | Obs    | Exp   | SMR  | 95% CI |      |
| All causes      | 295  | 268.7 | 1.10 | 0.98   | 1.23 | 207    | 202.9 | 1.02 | 0.89   | 1.17 |
| Selected causes |      |       |      |        |      |        |       |      |        |      |
| All cancers     | 106  | 83.9  | 1.26 | 1.03   | 1.53 | 46     | 52.0  | 0.89 | 0.65   | 1.18 |
| Liver           | 18   | 10.8  | 1.67 | 0.99   | 2.63 | 8      | 4.3   | 1.87 | 0.81   | 3.69 |
| Lung            | 27   | 17.3  | 1.56 | 1.03   | 2.27 | 5      | 5.8   | 0.86 | 0.28   | 2.01 |