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Relative survival after exposure to polychlorinated biphenyls and dioxins: A follow-up of Japanese patients affected in the Yusho incident ☆

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ABSTRACT

Objectives: Little information is available on conditional survival among Yusho patients, who were accidentally exposed to PCBs and other dioxin-related compounds. In this study, we estimated relative survival among Yusho patients to quantify time trends in excess mortality compared to the general population.
Methods: A total of 1664 Yusho patients (860 males, and 804 females) were analyzed as Yusho cohort subjects. Relative survival ratio (RSR) was calculated as a measure of patient survival.
Results: Overall, 1-, 5-, 10-, and 15-year RSRs were 1.00 (95% confidence interval (CI): 0.99, 1.00), 1.00 (95% CI: 0.99, 1.01), 0.99 (95% CI: 0.98, 1.00), and 0.99 (95% CI: 0.98, 1.01), respectively. We did not observe meaningful increases or decreases in RSRs in either sex, which remained the same in all age groups for 1-, 5-, 10-, and 15-year RSRs.
Conclusions: This study provides quantitative evidence that Yusho patients have no significant difference in relative survival compared with the general Japanese population. Our results suggest that PCBs and dioxin exposure confers no excess mortality. This information may be important for both the clinical management of and patient coping with Yusho disease.

1. Introduction

Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are unintended by-products of certain chemical processes involving chlorine and incineration processes (ATSDR (Agency for Toxic Substances and Disease Registry), 1994; ATSDR (Agency for Toxic Substances Disease Registry), 1998; ATSDR (Agency for Toxic Substances and Disease Registry), 2000). Specifically, PCDDs and PCDFs are by-products of combustion and of various industrial processes. PCBs were previously manufactured for a variety of industrial uses, notably as electrical insulators or dielectric fluids and specialized hydraulic fluids, although most countries banned their manufacture and use in the 1970s. These dioxins and dioxin-like compounds were widely spread in the environment during the last century, largely as a result of human activities.

In 1968, an incident involving mass accidental human exposure to PCBs and other dioxin-related compounds via the ingestion of contaminated rice oil occurred in western Japan (Masuda et al., 1985). As a result, more than 1800 patients suffered a range of symptoms, including acneiform eruptions; pigmentation of the skin, nails, and conjunctiva; increased discharge from the eyes; and numbness of the limbs (Urabe and Asahi, 1985; Ikeda, 1996). The syndrome resulting from this mass poisoning was named "Yusho," which means "oil disease" in Japanese. In the Yusho incident, PCBs used in a heat exchanger contaminated rice bran cooking oil during processing. As the PCBs had been thermally degraded, they were contaminated by PCDDs and PCDFs (Masuda et al., 1985). The Yusho incident has accordingly been used to evaluate the long-term adverse health effects associated with the ingestion of PCBs and dioxin-related compounds.

We previously conducted a 40-year follow-up study of mortality in the Yusho cohort (Onozuka et al., 2009). However, additional ongoing data will help evaluate the changing risk of death in each successive year after diagnosis of the disease: for patients who have survived for a specified time after diagnosis, the probability of surviving the following year provides information that is not available from overall survival. Termed conditional survival, the calculation of this variable provides an accurate evaluation of the patient's changing risk over time.

Abbreviations: PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls.

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Conditional survival measures relative survival, which provides a measure of mortality associated with a particular disease, without the need for information on the cause of death, which may be either recorded inaccurately or not at all. Relative survival is commonly used in population-based studies (Begg and Schrag, 2002; Lambert et al., 2010; Nelson et al., 2007), and in particular in national and international comparisons of cancer survival (Coleman et al., 2008), changes in survival over calendar time (Dickman and Adami, 2006), and exploration of potential risk factors for increased mortality. Use in therapeutic areas other than cancer is limited, however, and its use in Yusho studies has not been reported. Measurement of relative survival in Yusho patients would be particularly useful for decision making about treatments with severe side effects and in the planning of appropriate future care services.

In this study, we estimated relative survival among Yusho patients to evaluate if and to what extent these patients still have excess mortality compared to the general population.

2. Methods

The total number of Yusho patients listed in the Yusho case registry as of December 31, 2007, was 1918 (977 males and 941 females). Among these, 254 patients who were registered in the list after 1977 were excluded from the present analysis because they had not been diagnosed with Yusho from the beginning of the Yusho incident. Because the diagnostic criteria of Yusho were revised several times after the Yusho incident, affected patients who died prior to the official registration period might not have been included in this analysis, introducing bias into the results. Thus, we analyzed a total of 1664 patients (86.8% of Yusho patients). The members of this cohort had not received any special care, such as more frequent medical screenings, which might have resulted in early diagnosis of disease and therefore lower mortality.

The subjects were identified by name, date of birth, sex, address, and date and place of registration. Residence status, including survival, was confirmed through the residential registry. Survival status and the date of death for fatalities in Yusho patients were identified by inspection of the residential registry. Residency and death registration are mandatory in Japan under the Family Registration Law, and inspection of the resident registry is available to anyone under the resident registration law. Death certificates must be completed by licensed physicians, and are reliable in terms of quality and completeness.

We calculated survival time as beginning at the official registration date of the individual Yusho patient. This was because the detection of affected individuals at the time of exposure was complicated by the scattered distribution of contaminated rice oil throughout western Japan, and the technical impossibility of measuring PCBs and dioxins in the human body at the time of the incident. Thus, potential survival time between the exposure date and registration date might have been missed, and some affected individuals who survived might not have been identified.

Relative survival ratios (RSRs) were computed as measures of Yusho survival (Dickman and Adami, 2006; Henson and Ries, 1995). An important advantage of RSR is that it does not rely on the accurate classification of cause of death. Instead, RSR provides a measure of total excess mortality associated with the diagnosis of Yusho irrespective of whether the excess mortality was directly, indirectly, or not at all associated with Yusho. RSR is defined as the observed survival in a patient group, in which all deaths are considered events, divided by the expected survival of a comparable group from the general population. Expected survival was estimated using the Hakulinen method (Hakulinen, 1982) from Japanese population life-tables stratified by age, sex, and calendar time. One-, 5-, 10-, and 15-year RSRs with 95% confidence intervals (CI) were calculated for four age categories at the time of exposure (0 to 14, 15 to 29, 30 to 44, and >45 years). One-, 5-, 10-, and 15-year RSRs provide a measure of the fraction of Yusho patients who survived at 1, 5, 10, and 15 years, respectively. Poisson regression models using restricted cubic splines adjusted for sex and age group were applied to estimate smoothing estimates of RSR (Dickman et al., 2004). All statistical analyses were carried out using the Stata software application (ver. 11.1; Stata Corporation, College Station, TX, USA). The ethics committee of the Fukuoka Prefecture Environmental Health Research Advancement Committee approved this study on March 29, 2010 (reference number: 21-1777).

3. Results

Table 1 shows the distribution of subjects by age in 1968 and vital status in 2007. As of December 31, 2007, a total of 1664 Yusho patients (860 males and 804 females) were at risk. Approximately 32% of the cohort was under age 15 years in 1968. The mean age of Yusho patients alive in 2007 was 57.9 (standard deviation, 14.1) years in males and 61.3 (standard deviation, 15.2) in females. A total of 441 deaths (269 males and 172 females) occurred during the 40-year follow-up period. Follow-up with respect to vital status was complete [i.e., patients were followed until death or the end of the study (December 31, 2007)] for 1596 Yusho patients (95.9%). For patients lost to follow-up, survival time was censored at the date they were last known to be alive.

Overall, 1-, 5-, 10-, and 15-year RSRs were 1.00 (95% confidence interval (CI): 0.99, 1.00), 1.00 (95% CI: 0.99, 1.01), 0.99 (95% CI: 0.98, 1.00), and 0.99 (95% CI: 0.98, 1.01), respectively. Table 2 details the 1-, 5-, 10-, and 15-year RSRs and 95% confidence intervals stratified by sex and age categories. We did not observe meaningful increases or decreases in RSRs by sex or age for any of the 1-, 5-, 10-, or 15-year RSRs.

Figs. 1 and 2 show the model-based estimates of excess hazard ratios by age groups for male and female Yusho patients during the first 15 years and corresponding empirical estimates with 95% confidence intervals. Excess mortality was lower for females than males. In addition, although patients registered at an older age had higher excess mortality than those registered at a younger age, these excess mortality ratios were essentially the same as those of the general population.

4. Discussion

In this study, we provide quantitative evidence that Yusho patients have experienced no significant difference in relative survival compared with the general Japanese population. Further, we also found that excess mortality ratios were essentially the same as those of the general population. These findings, to our knowledge the first detailed analysis of time trends in long-term survival with this disease, suggest that PCBs and dioxin exposure does not confer excess mortality, and may be of value in both the clinical management of Yusho disease and in the ability of patients to cope with it.

Table 1
Demographic features of Yusho patients from 1968 to 2007.

	Males		Females	
	No.	(%)	No.	(%)
Age of the cohort in 1968, years				
0–14	291	(33.8)	240	(29.9)
15–29	148	(17.2)	164	(20.4)
30–44	210	(24.4)	208	(25.9)
45+	211	(24.5)	192	(23.9)
Total	860	(100.0)	804	(100.0)
Vital status of the cohort on December 31, 2007				
Alive	591	(68.7)	632	(78.6)
Dead	269	(31.3)	172	(21.4)
Total	860	(100.0)	804	(100.0)