



Regional impact of exposure to a polychlorinated biphenyl and polychlorinated dibenzofuran mixture from contaminated rice oil on stillbirth rate and secondary sex ratio



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ABSTRACT

Yusho disease, a polychlorinated biphenyl (PCB) and polychlorinated dibenzofuran (PCDF) mixed poisoning caused by contaminated rice oil, occurred in Japan in 1968. The evidence on reproductive outcome is limited. We therefore evaluated the regional impact of the exposure to the PCB and PCDF mixture on stillbirth rate and secondary sex ratio among the residents in two severely affected areas. We selected the regionally-affected towns of Tamanoura ($n = 4390$ in 1970) and Naru ($n = 6569$) in Nagasaki Prefecture, Japan, for study. We obtained data on stillbirths (spontaneous/artificial) and live-born births (total/male/female) from 1958 to 1994. For a decade and a half after the exposure, an increase in the rate of spontaneous stillbirths coincided with a decrease in the male sex ratio. Compared with the years 1958–1967, the ratios for spontaneous stillbirth rates were 2.16 (95% confidence interval: 1.58 to 2.97) for 1968–1977 and 1.80 (95% confidence interval: 1.25 to 2.60) for 1978–1987. The sex ratio (male proportion) was 0.483 (95% confidence interval: 0.457 to 0.508) in the first 10 years after exposure. Exposure to a mixture of PCBs and PCDFs affected stillbirth and sex ratio for a decade and a half after the exposure.

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1. Introduction

Yusho (oil disease) is a well-known polychlorinated biphenyl (PCB) and polychlorinated dibenzofuran (PCDF, or dioxins) mixed poisoning, caused by contaminated rice oil used for cooking (Kuratsune et al., 1996). The food poisoning spread mainly to the western part of Japan and continued at least during February to October 1968, when an order to prohibit the sale of the rice oil was issued (Kuratsune et al., 1996). The exposed patients developed acne-like skin lesions, pigmentation of the skin, nails, and conjunctiva, increased discharge from the eyes, and paresthesia of the extremities (Kuratsune et al., 1996). Although 1961 patients had been certified as “Yusho” patients as of 2011 (Furue, 2012), it was pointed out that there were many other uncertified patients (Shimoda, 2010). For example, the Ministry of Health and Welfare reported in 1969 that about 14,000 people claimed that they had been exposed (Ministry of Health and Welfare in Japan, 1969), and it is often the case that only one family member was certified as a patient whereas other members who ate the same rice oil were not. Indeed, even now, several uncertified patients are newly certified as “patients” every year.

Very few epidemiological studies of the Yusho event have evaluated the impact of exposure to the PCB and PCDF mixture on reproductive outcomes (Tsukimori et al., 2008, 2012; Yoshimura et al., 2001). A recent study that included 214 women with 512 histories of pregnancy, demonstrated an increased proportion of pregnancy loss within the first ten years (1968–1977) after poisoning (Tsukimori et al., 2008). With regard to secondary sex ratio (i.e., male proportion at birth), the evidence is inconclusive because of the small number of cases (Tsukimori et al., 2012; Yoshimura et al., 2001). These studies, however, only included the certified patients. Although this sampling method has merits, there are several limitations. First, the patients were certified based mainly on dermatological findings with an intake history of the contaminated rice oil (Kuratsune et al., 1996), thus, selection bias is not negligible. Second, the number of the participants was smaller than the actual exposure population. Third, as is usual with other individual studies, biased reporting is sometimes problematic. For example, in the abovementioned study, the authors obtained the participants' pregnancy histories (i.e., pregnancy loss) by interview (Tsukimori et al., 2008).

Ecological studies, although they have inherent shortcomings, may overcome some of the abovementioned limitations (Savitz, 2012). In this study, therefore, we evaluated the regional impact of the exposure to the PCB and PCDF mixture on stillbirth rate and secondary sex ratio among the residents in two severely affected areas.

Abbreviations: CI, confidence interval; PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran.

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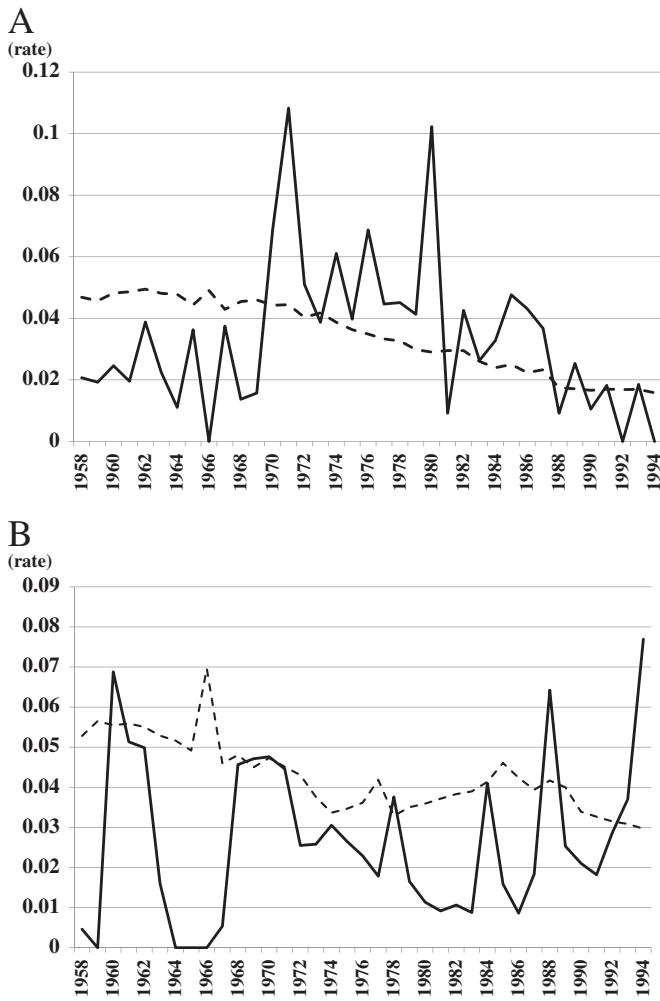


Fig. 1. Spontaneous (A) and artificial (B) stillbirth rates from 1958 to 1994. The rates of the exposure area (the towns of Tamanoura and Naru) are shown by the solid lines and those of Nagasaki Prefecture are shown by the dotted lines.

2. Material and methods

2.1. Study areas

We selected Tamanoura (n = 4390 in 1970) and Naru (n = 6569) in the Goto Archipelago in Nagasaki Prefecture (n = 1,570,245) as the exposure area, because these two towns are geographically distinct in terms of contamination. Although Nagasaki Prefecture included the exposure area, we adopted the population of Nagasaki Prefecture as the

reference population. Up to 2012, 543 and 167 certified cases were reported in each area (Tamanoura and Naru), and these represent 89% of the certified cases in the prefecture (Nagasaki Prefecture, 2012) and account for about 36% of total certified cases in Japan (Furue, 2012). Consequently, about 6.5% of the total population in 1970 in these towns had sufficient exposure history and clinical signs to be certified as cases. As mentioned, the number of uncertified cases may exceed that of certified ones. Moreover, these two towns are located on isolated islands; thus many residents in these areas used to buy a large amount of rice oil, then shared it among several families (Ministry of Health and Welfare in Japan, 1969). Hence, a large number of residents in the Tamanoura and Naru areas were considered to be exposed to the rice oil to some extent. This situation gave us a unique opportunity to explore geographically the health effects of the contaminated rice oil.

2.2. Outcomes

We obtained the numbers of stillbirths (spontaneous/artificial) and live-born births (total/male/female) in the exposure area (Tamanoura and Naru) and the reference population (Nagasaki Prefecture) from vital statistics during the period 1958–1994. As mentioned, an order to prohibit the sale of the rice oil was issued on October, 1968, and the subsequent health examinations were conducted between November and December, 1968, in Tamanoura and between April and May, 1969, in Naru (Shimoda, 2010). The sale or the use of the rice oil in the exposure areas is considered to have stopped by that time. In Japan, a stillbirth is legally defined as a fetal death at more than 12 weeks in gestation. Because the numbers of male/female live-born births were missing in the exposure area (only) in 1969, we deduced the missing numbers from the 1970 National Census.

2.3. Statistical analyses

We first plotted spontaneous and artificial stillbirth rates (stillbirths divided by sum of stillbirths and total live-born births) as well as sex ratios (male births divided by total live-born births) against each year from 1958 to 1994 in the exposure area with those of the reference population (Nagasaki Prefecture). We next divided the study period into four intervals (1958–1967, 1968–1977, 1978–1988 and 1989–1994), and compared stillbirth rates and sex ratios of post-exposure periods with those of the unexposed first 10 years (that is, from 1958 to 1967). We estimated 95% confidence intervals (CIs) applying a Poisson model for stillbirth rates and a binomial model for sex ratios (Rothman, 2012).

3. Results

Spontaneous and artificial stillbirth rates are shown in Fig. 1A and B, respectively. Although the spontaneous rates in the exposure area

Table 1
Spontaneous/artificial stillbirth^a rates and their rate ratios for the association between the periods and the rates.

	Periods			
	1958–1967	1968–1977	1978–1987	1988–1994
Number of live births	3036	1495	1064	488
Spontaneous stillbirths				
Number	73	80	47	6
Rate (95% CI)	0.023 (0.018 to 0.029)	0.051 (0.04 to 0.062)	0.042 (0.03 to 0.054)	0.012 (0.002 to 0.022)
Rate ratio (95% CI) ^b	1 (reference)	2.16 (1.58 to 2.97)	1.80 (1.25 to 2.60)	0.52 (0.23 to 1.19)
Artificial stillbirths				
Number	75	57	21	20
Rate (95% CI)	0.024 (0.019 to 0.03)	0.037 (0.027 to 0.046)	0.019 (0.011 to 0.028)	0.039 (0.022 to 0.057)
Rate ratio (95% CI) ^b	1 (reference)	1.52 (1.08 to 2.15)	0.80 (0.49 to 1.30)	1.63 (1.00 to 2.67)

CI: confidence interval.

^a Fetal death at more than 12 weeks in gestation.

^b Rate ratios were estimated using the period of 1958–1967 as a reference.

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