Environmental Research 120 (2013) 71–75

Contents lists available at SciVerse ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Mortality after exposure to polychlorinated biphenyls and dibenzofurans: 30 years after the "Yucheng Accident"

Ming-Chieh Li [a], Pei-Chien Tsai [b], Pau-Chung Chen [a], Chia-Jung Hsieh [a], Yue-Liang Leon Guo [c,*], Walter J. Rogan [d]

[a] Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taiwan
[b] Department of Medical Research, Kaohsiung Medical University Hospital, Taiwan
[c] Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine, Taiwan
[d] Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, USA

ARTICLE INFO

Article history:
Received 10 March 2012
Received in revised form
8 September 2012
Accepted 11 September 2012
Available online 29 September 2012

Keywords:
Yucheng
Dioxin
Polychlorinated biphenyls
Polychlorinated dibenzofurans
Standardized mortality ratio

ABSTRACT

Background: In 1979, approximately 2,000 people in central Taiwan were accidentally exposed to polychlorinated biphenyls and dibenzofurans due to ingestion of contaminated cooking oil. This event was called Yucheng, "oil-syndrome" in Chinese. We followed the exposed persons and compared their cause-specific mortality with that of neighborhood referents 30 years after the accident.
Methods: We obtained age- and gender-matched referents from the 1979 neighborhoods of the exposed people. Cause-specific mortality was compared between exposed subjects ($N=1803$) and their neighborhood referents ($N=5170$) using standardized mortality ratios (SMR). Total person-years for the Yucheng subjects and neighborhood referents were 48,751 and 141,774, respectively.
Results: The SMR for *all causes* (SMR=1.2, 95% CI: 1.1–1.3), *diseases of the circulatory system* (SMR=1.3, 95% CI: 1.0–1.6), and *diseases of the musculoskeletal system and connective tissue* (SMR=6.4, 95% CI: 2.8–12.7) were elevated in Yucheng subjects. Among Yucheng males, the SMRs for *diseases of the digestive system* (SMR=1.9, 95% CI: 1.2–2.8), *malignant neoplasm of stomach* (SMR=3.5, 95% CI: 1.5–7.0), and *malignant neoplasm of lymphatic and hematopoietic tissue* (SMR=3.0, 95% CI: 1.1–6.6) were increased. The SMR for total neoplasms was increased (SMR=1.3, 95% CI: 0.9–1.7).
Conclusion: We conclude that exposure to PCBs/PCDFs at levels that produced symptoms in many affects mortality patterns 3 decades after exposure.

1. Introduction

In 1979, there was an outbreak of severe acne, skin pigmentation, and conjunctivitis in central Taiwan. Most of the cases had consumed the same brand of cooking oil, bought at the same stores (Hsu et al., 1985). The illness, and its relation to cooking oil consumption, resembled a form of polychlorinated biphenyl (PCB) poisoning (called "Yusho," oil disease in Japanese) that had occurred in western Japan in 1968 (Kuratsune et al., 1972), and oil and blood samples sent to Tokyo for analysis had high concentrations of PCBs. Yu-Cheng ("oil disease" in Chinese) thus became the second recorded disease outbreak due to rice bran cooking oil contaminated by PCBs during manufacture (Hsu et al., 1985). Although about 2000 persons registered with health agencies as being exposed after each episode, the exact number of victims is unknown.

PCBs are compounds with 2 linked phenyl rings and variable degrees of chlorination. From the 1930 s until the mid-1970 s, they were used worldwide as insulators, dielectrics, and heat exchangers in heavy electrical equipment. It was a heat exchange machine that leaked the PCBs into the cooking oil. PCBs were discarded without thought for environmental consequences, and their persistence and fat solubility led to widespread contamination of the food chain. By the time of their ban in the US, the concentrations of PCBs detected in human fat samples and the fat of breast milk were surpassed among pollutants only by those of dichlorodiphenyltrichloroethane (DDT) (Jensen, 1983).

The cooking oil that caused the Asian outbreaks was contaminated not only with PCBs but also with polychlorinated dibenzofurans (PCDFs). During an average of 9 months of exposure, the victims in Taiwan consumed about 1 g of PCBs and 3.8 mg of PCDFs (Lan et al., 1981). Even 15 years after the exposure, serum concentrations of PCBs and PCDFs were 20–40 times and 40–60 times higher than background (Lambert et al., 2006). The Taiwan Provincial Department of Health set up and maintained a Yucheng registry that included 1,991 directly exposed subjects, and 70 children exposed in utero (Hsu et al., 1985).

PCBs cause cancer in laboratory experiments, but studies of workers with occupational exposure have been inconsistent. Although the International Agency for Research on Cancer does

* Correspondence to: No.1, Section 1, Ren-ai Rd., Zhongzheng Dist., Taipei City 100, Taiwan. Fax: +886 2 23278515.
E-mail address: leonguo@ntu.edu.tw (Y.-L. Leon Guo).

0013-9351/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.envres.2012.09.003

classify one specific congener, PCB 126, as a "known" human carcinogen, they classify PCBs as a whole as "probable" human carcinogen (International agency for research on cancer, 2012). PCBs and PCDFs are members of a group of chemicals, the polychlorinated aromatics, that include the very toxic 2,3,7,8-tetrachlorodibenzo-p-dioxin, called TCDD or simply "dioxin". Much of the toxicity of the different chemicals is similar, and is thought to involve occupancy of the Ah receptor. IARC considers TCDD a known human carcinogen (IARC 2012), based on occupational studies showing increased overall cancer mortality, as well as excess cancer in the town of Seveso, Italy, where an explosion at a chemical plant led to widespread dioxin exposure.

Unlike the occupational cohorts, many of the victims of the Asian outbreaks were symptomatic, and so it seemed likely that the doses to which they were exposed could produce a detectable cancer excess. By 1998, although mortality studies of the Yusho and Yucheng cohorts both showed excess mortality for non-malignant liver disease, only the Yusho cohort showed an excess of liver cancer (Ikeda et al., 1987; Yu et al., 1997). We anticipated that the discrepancy in findings between Yusho and Yucheng would resolve with further follow-up. However, when we updated our report in 2007, we did not observe any increase in liver cancer, but did see an unanticipated excess of deaths from systemic lupus erythematosis (Tsai et al., 2007). These studies used the Taiwan population as the referents, and we were concerned that regional or socioeconomic variation might have biased the findings. Here, we add 4 more years of mortality data, which increases the number of deaths from 215 to 295, and, for the first time, use the neighborhood controls (Guo et al., 1999) from our morbidity studies as the referents.

2. Materials and methods

The follow-up study of mortality status has been approved by the Institutional Review Board of the National Taiwan University Medical Center. We began with the Yucheng Registry (Hsu et al., 1985) and the list of neighborhood referents that was described previously (Yu et al., 1997; Guo et al., 1999). When the PCB poisoning was discovered in 1979, a registry of subjects was set up by the Taiwan Provincial Department of Health (Guo et al., 1994). The criteria used to identify subjects included consumption of brands of rice oil produced in the factory known as the source of the contamination, and the development of skin, nail, eye, and other symptoms from January to October 1979. About 10% of persons in the registry gave a history of PCB exposure and had elevated serum PCB concentrations but were asymptomatic (Hsu et al., 1985).

A total of 2,061 subjects were included in the Yucheng registry by 1983, including 70 children born to exposed mothers. Among the 1,991 in the list who were directly exposed, 154 did not have an address, and thus could not be traced further. These individuals were excluded from the first study of mortality in 1992 (Yu et al., 1997). Each person in Taiwan is assigned a national identification number when registering their first permanent address. We had the national identification number for all participants. A typical national identification number has one Latin character and nine digits. The last digit of the national identification number is a check digit, which is generated from the letter and the other digits based on a formula. The check digit helps identify legitimate national identification numbers. Among the national identification numbers listed for the Yucheng subjects, 34 had check digits that were inconsistent with the rest of the number and were excluded. We thus had 1,803 exposed Yucheng subjects for this study.

The neighborhood referents were recorded as residents, in 1979, of the same community (usually on the same street), had the same gender, had birthdays within 3 years of the Yucheng subjects' birthday, and were not themselves in the registry. We attempted to identify three referents for each Yucheng subject, and found 5,519 eligible persons. Among them, 8 had no date of birth recorded, and 98 were born after June 30, 1978, during or after the incident, and so had been selected in error and were excluded. An additional 243 had national identification numbers with an inconsistent check digit, and they were excluded, leaving 5,170 neighborhood referents. The final ratio of Yucheng subjects to neighborhood referents was 1: 2.9. We previously reported that these referents were of similar education, occupation, and socioeconomic status as the Yucheng subjects (Guo et al., 1999).

We compared the national identification numbers of these two groups with the national mortality registry to determine vital status, and, if deceased, date of death and cause of death. In Taiwan, it is mandatory to report deaths within 1 month to the local registration office responsible for the area in which the deceased resided. These reports are believed to be complete. The cause of death was coded according to the ninth revision of the International Classification of Diseases (ICD-9). Unfortunately, the national mortality registry did not contain national identification numbers until 1985. To address this issue, we used another mortality registry to obtain identification numbers. The Taiwan Ministry of the Interior had established a separate death registry based on death certificates. This registry had complete identification numbers, but lacked the ICD-9 codes. We submitted the identification numbers to the Ministry of Interior's registry to determine fact and date of death, and then, using them plus the date of birth and area code of the decedents, matched to the national mortality registry for ICD-9 cause of death. We only accepted exact matches. This yielded a valid match for 89% of all decedents from 1980–84.

Among the 1,803 Yucheng subjects and 5,170 neighborhood referents, 295 and 757 had died between January 1, 1980 and December 31, 2008, respectively. The overall and cause-specific mortality of the Yucheng subjects were compared to neighborhood referents. Each study subject contributed observed person-time from January 1, 1980 to the date of the end of follow-up (December 31, 2008) or through their date of death.

We used an age-stratified method to calculate standardized mortality ratio (SMR). The person-years at risk for all subjects were combined into gender, 5-year age, and 1-year calendar time-specific groups. The accumulated person-years were then multiplied by the gender, age, calendar time, and cause-specific neighborhood referents' mortality rates to yield the expected numbers of cause-specific deaths. The observed number of cause-specific deaths was then divided by the expected number of cause-specific deaths to yield the SMR. The 95% confidence intervals around the SMRs were estimated based on the Fisher mid-P exact confidence intervals. Mortality data also were analyzed separately by gender. For those national identification numbers that appeared in the mortality database, but lacked an ICD-9 code, the person-time of observation was still included when calculating SMRs.

3. Results

A total of 1,803 Yucheng subjects with 48,751 person-years and 5,170 neighborhood referents with 141,774 were at risk from January 1, 1980 to the dates of death or December 31, 2008. A total of 295 Yucheng subjects and 757 neighborhood referents died during that time. Table 1 shows that there was a similar age and gender distribution for Yucheng subjects and neighborhood referents.

Table 2 shows results for all-cause and cause-specific mortality. The *all-cause* standardized mortality ratio was elevated for all Yucheng subjects and for males specifically. Elevations occurred among all Yucheng subjects for *diseases of the circulatory system* (SMR=1.3, 95% CI: 1.0–1.6). In *diseases of the circulatory system*, the SMRs for *acute myocardial infarction* (SMR=2.0, 95% CI: 1.0–3.4), *other forms of heart disease* (SMR=2.3, 95% CI: 1.4–3.5), *cardiac dysrhythmias* (SMR=5.8, 95% CI: 1.8–13.9), and *late effects of cerebrovascular disease* (SMR=2.9, 95% CI: 1.3–5.7) were increased. The SMR for *diseases of the musculoskeletal system* and *connective tissue* (SMR=6.4, 95% CI: 2.8–12.7) was much increased due to *systemic lupus erythematosus* mortality (1 male and 5 females in Yucheng subjects, 0 in neighborhood referents).

Among Yucheng males, the SMRs for *diseases of the digestive system* (SMR=1.9, 95% CI: 1.2–2.8), and *injury and poisoning* (SMR=1.5, 95% CI: 1.0–2.1) were increased. In *diseases of the digestive system*, the SMR for *chronic liver disease and cirrhosis* (SMR=2.5, 95% CI: 1.5–3.9) was increased. Although the SMR for *disease of the circulatory system* was not increased, the SMRs for *acute myocardial infarction* (SMR=3.3, 95% CI: 1.6–6.4) and *other forms of heart disease* (SMR=2.2, 95% CI: 1.2–3.8) were increased. Although the SMR for all neoplasms was not increased, the SMRs for *malignant neoplasm of stomach* (SMR=3.5, 95% CI: 1.5–7.0) and *malignant neoplasm of lymphatic and haematopoietic tissue* (SMR=3.0, 95% CI: 1.1–6.6) were increased. The SMR for *diabetes mellitus* was decreased (SMR=0.3, 95% CI 0.1–0.9).

Among Yucheng females, the SMRs for *diseases of the circulatory system* (SMR=1.5, 95% CI: 1.0–2.1) and *musculoskeletal system and connective tissue* (SMR=16.5, 95% CI: 6.7–34.3) were increased. In *disease of the circulatory system*, the SMRs for *other*