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Mortality after exposure to Polychlorinated Biphenyls and Dibenzofurans: 30 years after the "Yucheng Accident"

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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.

Keywords

Yucheng; dioxin; polychlorinated biphenyls; polychlorinated dibenzofurans; standardized mortality ratio

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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 1930s until the mid-1970s, 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 1g 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 (IARC) does classify one specific congener, PCB 126, as a "known" human carcinogen, they classify PCBs as a whole as "probable" human carcinogens (IARC 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.

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. 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).

Atotal 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 1 English letter and 9 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.

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 forms of heart disease* (SMR=2.4, 95% CI: 1.2–4.5), *cardiac dysrhythmias* (SMR=9.6, 95% CI: 2.4–26.0),

and *late effects of cerebrovascular disease* (SMR=5.4, 95% CI: 1.7–13.1) were increased. In *disease of musculoskeletal system and connective tissue*, the relative mortality from systemic lupus erythematosus was very high (5 in Yucheng females, 0 in neighborhood referents).

DISCUSSION

We did a follow-up study comparing the mortality experience of persons with high exposures to PCBs and PCDFs 30 years previously with that of a neighborhood referent group. We found increased all-cause mortality, and specific increases in mortality from *malignant neoplasms of the stomach*, and of *lymphatic and haematopoietic tissue; diseases of the circulatory system*, *diseases of the digestive system*, and *diseases of the musculoskeletal system and connective tissue*. Compared with our previous study (Tsai, et al., 2007), new findings here are increased mortality from *all causes*, malignant neoplasms, and *diseases of the circulatory system* (Table 3). While the increase is mostly because there have been more deaths, we believe that the neighborhood referents form a better control group than the national population. In Taiwan in the 1980s, much of the population resided in the 2 largest cities – Taipei in the north and Kaohsiung in the south. Yucheng occurred in central Taiwan, in relatively rural Taichung and Changhua counties. Thus the national mortality rates, dominated by the experience of the cities, were not reflective of the demographic characteristics of the Yucheng subjects. It has always been desirable to have a local referent for mortality, but, until recently, there were too few deaths to allow stable comparisons.

This is the first time the Yucheng follow-up has showed elevated mortality due to malignant neoplasms. They occur mostly in males, which is also true in the 40 year follow-up from Yusho in Japan(Onozuka et al., 2009). The predominant excesses in Japan are in liver and lung cancer, with a small increase in stomach cancer, whereas we see excesses in stomach and haematopoietic malignancies, and no liver cancer excess. It may be worth noting that, throughout follow-up, there has been a larger excess of non-malignant liver disease mortality, but not liver cancer mortality, among Yucheng subjects compared with Yusho subjects from Japan. The differences might be due to the differences in the degree and character of the contaminants in the rice oil (Masuda et al., 1985), or to the different prevalence of some other etiologic factor, such as aflatoxin (Montesano, R. et al., 1997). or hepatitis virus (CDC., 2008) between Japan and Taiwan. However, the mechanisms underlying both the difference in cancer sites and the much later appearance of malignancy in Taiwan are still unclear.

Several cohorts with exposure to high levels of dioxin-like chemicals show elevated risks of cancer of the lymphatic and hematopoietic system (Steenland et al., 1999; Flesch-Janys et al., 1998; Bertazzi et al., 2001; Bertazzi et al., 1989; Consonni et al., 2008; Kimbrough et al., 2003; Gustavsson et al., 1986; Gustavsson et al., 1997). For stomach cancer, a mortality study of capacitor manufacturing workers found elevated risk in male workers (Mallin et al., 2004). Incidence of stomach cancer was increased in the highly exposed residents living around a former PCB production site (Pavuk et al., 2004).

We also found excess mortality from circulatory diseases, specifically acute myocardial infarction and other forms of heart disease, but not cerebrovascular disease. Among other forms of heart diseases, death from cardiac dysrhythmias was elevated in Yucheng subjects. A systematic review suggested an association between dioxin exposure and mortality from ischemic heart disease, and possibly all cardiovascular disease (Humblet et al., 2008). People living in areas contaminated with persistent organic pollutants, including PCBs and dioxins/furans, had elevated rates of hospital discharge for coronary heart disease and acute

myocardial infarction compared to those living in non-contaminated areas (Sergeev and Carpenter, 2005). In the Ranch Hand cohort, exposed to Agent Orange contaminated with TCDD, increased mortality from circulatory diseases was found at 20 years of follow-up (Ketchum and Michalek, 2005). In Yusho subjects exposed to PCBs/PCDFs in Japan, elevated mortality from heart disease was found among females in the period 25–29 years after the incident, but not for other periods (Onozuka et al., 2009). Another study of Yusho (Kashima et al., 2011) reported an increased SMR for cardiovascular disease shortly after the exposure. Our findings of increased mortality from circulatory diseases support the association of exposure to dioxin-like chemicals with cardiovascular mortality.

Among Yucheng subjects, the SMR for systemic lupus erythematosus was quite increased, with one among Yucheng males, five among Yucheng females; and zero among the neighborhood referents. This finding was consistent with the previous study using the general population as reference group (Tsai et al., 2007). In the Yusho cohort, no mortality due to systemic lupus erythematosus was reported. However, Shimizu reported higher nitrotyrosine in the serum of Yusho subjects (Shimizu et al., 2008). Nitrotyrosine is a marker of protein oxidation in sera(Morgan et al., 2004; Morgan et al., 2005; Grune et al., 1997) and is associated with disease severity in patients with lupus(Morgan et al., 2005). Further study is warranted to determine whether nitrotyrosine was elevated in Yucheng subjects, which might have contributed to the development of systemic lupus erythematosus.

Diabetes has higher prevalence among Yucheng females, but not males (Wang et al., 2008). However, diabetes mortality was not higher in females and lower in males. Possible causes of these observations include the low case-fatality rate for diabetes, making estimates of the SMR unstable, and assigning diabetes-related cardiovascular disease to the cardiovascular disease category.

There are strengths in this investigation. The establishment of a registry soon after the exposure allowed for relatively complete and unbiased ascertainment of exposed subjects for mortality studies. The use of neighborhood referents limited bias due to socioeconomic or geographic factors. There are also limitations in this study. First, in the national mortality registry of 1980–84, only 89% of all decedents had complete national identification numbers and ICD-9 codes. Thus, some deceased subjects could have been misclassified as being alive. This would affect both Yucheng subjects and referents, and should cause underestimation of deaths in both groups. Therefore, it is unlikely to produce high SMRs in the Yucheng group. Second, some subjects were excluded due to wrong or missing national identification numbers. This might have caused underestimation of deaths in both groups. Third, although using neighborhood referents may minimize some bias due to socioeconomic or geographic factors, confounding due to other factors such as medical history, smoking status, alcohol drinking, and physical activity could not be controlled. Fourth, selection bias cannot be ruled out, because the selection processes of Yucheng subjects and their neighborhood referents were different. Since one of the selection criteria for the Yucheng subjects was presence of symptoms related to PCB exposure, it is possible that those included in the registry were at higher risk of having some illnesses. However, the most prevalent symptoms among the Yucheng subjects in the registry were skin (chloracne and hyperkeratosis), nail (discoloration), and eye symptoms (discharge and eyelid swelling). These were more likely directly related to PCB poisoning, and less likely early signs of other important illnesses but unrelated to PCBs. We cannot exclude the possibility that persons with exposure and symptoms were more likely to be registered than those without. There was, however, much local publicity at the time about the etiology of the illness and the specific sites where the contaminated oil was sold or used. About 10% of those registered had a history of consuming the oil and/or elevated serum levels of PCBs. We do not believe there were many people with high PCB exposure and no symptoms; if there

were, our estimates of the SMRs are too high. Finally, some of the referents may have been exposed to the contaminated oil without their knowledge. We believe this to be unlikely. The provincial health department announced the etiology of the episode through mass media and local health units in October, 1979, and offered analysis of serum for PCBs to anyone who thought they had been exposed. (Hsu et al., 1985). In 1992, pooled neighborhood blood samples from 56 women were analyzed for PCBs and PCDFs, which showed background exposure only (Guo et al., 1997). If there were many people with exposure who did not participate in the registry but suffered ill effects from their exposure, then our estimates of the SMRs are too low. In conclusion, 30 year follow-up of mortality in the Yucheng cohort as compared to a neighborhood reference group found increased deaths from liver diseases, cardiovascular diseases, systemic lupus erythematosus, and neoplasms including stomach cancer and lymphatic and hematopoietic tissue cancer. Additional follow up is necessary to confirm the present findings.

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Table 1

Demographic description in 1980 of Yucheng subjects and neighborhood referents.

	Status of January 1, 1980	
Types	**Yucheng subjects (N=1,803)**	**Neighborhood referents (N=5,170)**
Age		
0–19	792 (44%)	2,173 (42%)
20–39	603 (33%)	1,828 (35%)
40–59	343 (19%)	980 (19%)
60+	65 (4%)	189 (4%)
Gender		
Male	830 (46%)	2,369 (46%)
Female	973 (54%)	2,801 (54%)
Person-year	48,751	141,774
Deceased	295	757

N: Number

Table 2

Observed and expected numbers of deaths and standardized mortality ratio (SMR) for overall and cause-specific deaths among 1,803 Yucheng subjects, from January 1, 1980 to December 31, 2008.

Cause of death (ICD 9)	Males			Females			Total		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
All causes (001–999)	178	143.9	**1.2 (1.2–1.4)**	117	105.4	1.1 (0.9–1.3)	295	248.9	**1.2 (1.1–1.3)**
Infectious and parasitic diseases (001–139)	9	6.0	1.5 (0.7–2.8)	2	3.5	0.6 (0.1–1.9)	11	9.4	1.2 (0.6–2.0)
Neoplasms (140–239)	46	36.4	1.3 (0.9–1.7)	21	26.4	0.8 (0.5–1.2)	67	62.6	1.1 (0.8–1.4)
Malignant neoplasm of liver and intrahepatic bile ducts(155)	4	9.0	0.4 (0.1–1.1)	6	2.8	2.1 (0.9–4.5)	10	11.7	0.9 (0.4–1.5)
Malignant neoplasm of trachea, bronchus and lung (162)	10	6.5	1.5 (0.8–2.7)	1	2.8	0.4 (0.0–1.7)	11	10.2	1.1 (0.6–1.9)
Malignant neoplasm of stomach (151)	7	2.0	**3.5 (1.5–7.0)**	1	2.0	0.5 (0–2.5)	8	4.0	2.0 (0.9–3.8)
Malignant neoplasm of lymphatic and haematopoietic tissue (200–208)	5	1.7	**3.0 (1.1–6.6)**	0	1.6	--	5	3.3	1.5 (0.6–3.4))
Malignant neoplasm of thyroid gland (193)	0	0	--	2	1.0	2.0 (0.3–6.7)	2	0.9	2.2 (0.4–7.2)
Malignant neoplasm of female breast (174)	0	0	--	4	3.6	1.1 (0.4–2.7)	--	--	--
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	7	10.3	0.7 (0.3–1.3)	11	9.7	1.1 (0.6–2.0)	18	20.0	0.9 (0.5–1.4)
Diabetes mellitus (250)	3	9.4	**0.3 (0.1–0.9)**	9	9.5	1.0 (0.5–1.7)	12	19.0	0.6 (0.3–1.1)
Mental disorders (290–319)	0	1.3	--	0	0.3	--	0	1.3	--
Diseases of the nervous system and sense organs (320–389)	1	1.9	0.5 (0.0–2.6)	1	1.6	0.6 (0.0–3.2)	2	3.5	0.6 (0.1–1.9)
Disease of the circulatory system (390–459)	38	32.0	1.2 (0.9–1.6)	33	22.2	**1.5 (1.0–2.1)**	71	54.5	**1.3 (1.0–1.6)**
Acute myocardial infarction (410)	8	2.4	**3.3 (1.6–6.4)**	3	3.2	0.9 (0.2–2.5)	11	5.6	**2.0 (1.0–3.4)**
Other forms of heart disease (420–429)	11	5.0	**2.2 (1.2–3.8)**	9	3.7	**2.4 (1.2–4.5)**	20	8.7	**2.3 (1.4–3.5)**
Cardiac dysrhythmias (427)	1	0.3	3.0 (0.1–14.4)	3	0.3	**9.6 (2.4–26.0)**	4	0.7	**5.8 (1.8–13.9)**
Late effects of cerebrovascular disease (438)	3	1.8	1.7 (0.4–4.5)	4	0.7	**5.4 (1.7–13.1)**	7	2.4	**2.9 (1.3–5.7)**
Diseases of the respiratory system (460–519)	7	9.7	0.7 (0.3–1.4)	7	7.2	1.0 (0.4–1.9)	14	16.7	0.8 (0.5–1.4)
Disease of the digestive system (520–579)	23	12.1	**1.9 (1.2–2.8)**	9	11.8	0.8 (0.4–1.4)	32	24.1	1.4 (0.9–1.9)
Chronic liver disease and cirrhosis (571)	16	6.5	**2.5 (1.5–3.9)**	3	5.9	0.5 (0.1–1.4)	19	12.4	1.5 (1.0–2.3)
Disease of the genitourinary system (580–629)	6	3.7	1.6 (0.7–3.4)	6	6.2	1.0 (0.4–2.0)	12	9.9	1.2 (0.7–2.1)
Diseases of the skin and subcutaneous tissue (680–709)	1	0.3	3.1 (0.2–15.4)	0	0.9	--	1	1.2	0.8 (0.0–4.2)
Diseases of the musculoskeletal system and connective tissue (710–739)	1	0.7	1.4 (0.1–6.7)	6	0.4	**16.5 (6.7–34.3)**	7	1.1	**6.4 (2.8–12.7)**
Systemic lupus erythematosus (710)	1	0	--	5	0	--	6	0	--
Symptoms, signs, and ill-defined conditions (780–799)	8	8.6	1.0 (0.4–1.8)	7	4.9	1.4 (0.6–2.8)	15	13.2	1.1 (0.7–1.8)

Cause of death (ICD 9)	Males			Females			Total		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Injury and poisoning (800–999)	27	18.5	**1.5 (1.0–2.1)**	12	9.0	1.3 (0.7–2.3)	39	27.3	**1.4 (1.0–1.9)**

ICD-9: International Classification of Diseases, ninth revision; **O**: Observed numbers; **E**: Expected numbers **95% CI**=95% confidence interval calculated based on Mid-P tests; **Bolded text**: The ratio of Yucheng observed number of deaths over expected number of deaths is significant.

Table 3

The differences in results using the different reference populations.

Types of mortality	Reference population	
	Neighborhood referents	**Taiwan general population**
All causes	Increase in all Yucheng subjects and Yucheng males	Not different
Malignant neoplasms	*Malignant neoplasm of stomach* and Malignant neoplasm of *lymphatic and hematopoietic tissue* were increased in Yucheng males	Malignant neoplasm of *lymphatic and hematopoietic tissue* was slightly increased in Yucheng males, but did not reach statistical significant.
Disease of the circulatory system	Increase in all Yucheng subjects and Yucheng females	Slightly increase in Yucheng females, but did not reach statistical significant.
Disease of the digestive system	Increase in Yucheng males, especially for *chronic liver disease and cirrhosis*	Increase in all Yucheng subjects and Yucheng males, especially for chronic liver disease and cirrhosis
Diseases of the musculoskeletal system and connective tissue	Increase in all Yucheng subjects and Yucheng females, especially for systemic lupus erythematosus	Increase in all Yucheng subjects and Yucheng females, especially for systemic lupus erythematosus