Chapter 10

Survival of Patients

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An analysis of the deaths seen among Yusho patients over the past 22 years is without doubt important not only to understand the possible human effects of a prolonged exposure to PCBs, PCDFs and other chlorinated hydrocarbons, but also to provide the victims with better health care. A cohort analysis was therefore made on their mortality.

The total number of patients officially registered as suffering from Yusho by March 31, 1990 was 1,870. Of these, 1,821 registered by March 31, 1983 were investigated regarding their survival. Information on their name, date of birth, sex, address, date of registration, and place where they were registered was obtained from the Ministry of Health and Welfare and their vital status on March 31, 1990 was confirmed by the health departments of the municipalities where patients had lived or still were living, and copies of the death certificates for the deceased were also collected by these departments. Information on the serum PCB levels and gas chromatographic patterns of the PCBs was obtained from the health departments of the municipalities for 865 patients. The underlying causes of deaths seen before 1979 were identified according to the 8th revision of ICD while those of deaths seen from 1979 and after were based on the 9th revision of ICD.

10.1. Comparison of Yusho Patients' Mortality with the Standard Japanese Mortality (O/E Ratio)

In our preliminary study, a cohort analysis was made for the deaths seen among the patients from 1968 to 1983 (Ikeda et al., 1986). In the present study, the observation period was extended up to 1990 and two cohorts of Yusho patients, that is, all Yusho patients and a group of Yusho patients for whom PCB information was available, were followed (Table 10.1). The first cohort, consisting of 1,815 patients (816 males and 899 females), was observed from the date of official registration of each patient to the end of March 1990, with the average duration of observation being about 17.2 years. The second cohort, consisting of 865 patients (407 males and 458 females) and which was a part of the first one, was observed from the year of PCB measurement made for each patient up to March 31, 1990, with the average duration of observation being 12.6 years. The deaths seen among the cohorts during the observation period were compared with the expected number of deaths, which was calculated by applying the national age, sex, and cause specific death rates in 1970, 1975, 1980, 1985, and 1990 to the person years at risk. The number of deaths observed totaled 200, including 127 males and 73 females, as shown in

Table 10.1. Observed Person Years at Risk

Cohorts	No. of patients	1968–1972	1973–1977	1978–1982	1983–1987	1988–1990	Total
Patients with PCB data							
Male	407	—	691	1,713	1,960	889	5,253
Female	458	—	679	1,782	2,234	1,028	5,723
All patients							
Male	916	2,022	3,517	4,156	4,105	1,856	15,656
Female	899	2,066	3,412	4,039	4,243	1,940	15,700

Table 10. 2. The male deaths were slightly higher than expected and the difference was statistically significant, while female deaths were less than expected, with no statistical significance. Neither a significantly elevated nor lowered mortality was seen for tuberculosis, diabetes, heart diseases, hypertensive diseases, pneumonia and bronchitis, gastric and duodenal ulcer, kidney diseases, or accidents. Deaths from cerebrovascular diseases were considerably less than expected in both males and females, but significantly so only in females.

For deaths from cancer at all sites, a significantly increased mortality was seen in males but not in females. Neither a significantly increased nor decreased mortality was seen for cancer of the esophagus, stomach, rectum and colon, lung, pancreas, breast, and uterus, or for leukemia.

For cancer of the liver, increased mortality was noted in males, 12 observed deaths against 3.58 expected (O/E ratio = 3.36) and in females, three observed deaths against 1.33 expected (O/E ratio = 2.26), but the increase was only statistically significant in males. Since about 45% and 40% of the patients are residents of Fukuoka and Nagasaki Prefectures, respectively, where liver cancer is known to be prevalent, an additional analysis was made by calculating the expected number of deaths on the basis of liver cancer death rates in these prefectures instead of using the national average death rates. However, a significantly increased mortality was still observed in males (Observed = 12, Expected = 5.22, O/E ratio = 2.30, $p < 0.05$) but not in females (Observed = 3, Expected = 1.77, O/E ratio = 1.69). It is notable that the deaths from chronic liver diseases and cirrhosis were also slightly increased in both males and females, although the increase was not statistically significant (Table 10.2). The above findings were basically the same as those obtained in our preliminary study.

Table 10.2. The Observed and Expected Number of Deaths and SMR (O/E) by Cause of Death (All Patients)

Cause of death	ICD-8	ICD-9	Male			Female		
			Observed	Expected	O/E	Observed	Expected	O/E
Total			127	107.29	1.18	73	81.52	0.90
Tuberculosis	010–019	010–018	1	1.54	0.65	0	0.58	0.00
Malignant neoplasms	140–209	140–208	45	29.03	1.55[a]	13	19.18	0.68
Esophagus	150	150	2	1.40	1.43	1	0.30	3.29
Stomach	151	151	10	8.97	1.12	1	5.12	0.20
Rectum, sigmoid colon and anus	154	154	2	1.20	1.67	0	0.82	0.00
Liver	155, 197.7, 197.8	155, 199.1c	12	3.58	3.36[a]	3	1.33	2.26
Pancreas	157	157	2	1.47	1.36	1	1.01	0.99
Lung, trachea and bronchus	162	162	9	4.96	1.81	0	1.69	0.00
Breast	174	174, 175	—	—	—	1	1.30	0.77
Uterus	180–182	179–182	—	—	—	2	1.53	1.31
Leukaemia	204–207	204–208	2	0.78	2.57	0	0.56	0.00
Diabetes	250	250	1	1.22	0.82	0	1.18	0.00
Heart diseases	393–398, 410–429	393–398, 410–429	20	17.44	1.15	16	14.51	1.10
Hypertensive diseases	400–404	401–405	1	1.57	0.64	1	1.91	0.52
Cerebrovascular diseases	430–438	430–438	14	20.50	0.68	7	17.82	0.39[a]
Pneumonia and bronchitis	480–486, 490, 491, 466	480–486, 490, 491, 466.0	6	6.57	0.91	1	4.60	0.22
Gastric and duodenal ulcer	531–533	531–533	0	0.93	0.00	1	0.50	2.02
Chronic liver diseases and cirrhosis	794	797	6	3.61	1.66	3	1.30	2.31
Nephritis, nephrose syndrome and nephrose	580–584	580–589	1	1.58	0.63	3	1.45	2.07
Accidents	E800–E949	E800–E949	10	6.86	1.46	2	2.13	0.94

[a]: $p < 0.01$

Unknown cause of death: male 9, female 12.

Table 10.3. The Observed and Expected Number of Deaths and SMR (O/E) by Cause of Death (Patients with Data for Blood PCBs)

Cause of death	ICD-8	ICD-9	Male			Female		
			Observed	Expected	O/E	Observed	Expected	O/E
Total			30	45.29	0.66[a]	21	32.35	0.65[a]
Tuberculosis	010–019	010–018	1	0.52	1.94	0	0.18	0.00
Malignant neoplasms	140–209	140–208	8	13.47	0.59	4	8.96	0.45
Esophagus	150	150	0	0.65	0.00	0	0.13	0.00
Stomach	151	151	2	3.87	0.52	1	2.18	0.46
Rectum, sigmoid colon and anus	154	154	0	0.55	0.00	0	0.38	0.00
Liver	155, 197.7, 197.8	155, 199.1c	2	1.73	1.16	1	0.65	1.54
Pancreas	157	157	1	0.72	1.39	0	0.52	0.00
Lung, trachea and bronchus	162	162	0	2.50	0.00	0	0.86	0.00
Breast	174	174, 175	—	—	—	0	0.64	0.00
Uterus	180–182	179–182	—	—	—	1	0.65	1.54
Leukaemia	204–207	204–208	1	0.31	3.23	0	0.24	0.00
Diabetes	250	250	0	0.53	0.00	0	0.51	0.00
Heart diseases	393–398, 410–429	393–398, 410–429	3	7.64	0.39	4	5.99	0.67
Hypertensive diseases	400–404	401–405	1	0.53	1.89	1	0.57	1.75
Cerebrovascular diseases	430–438	430–438	3	7.92	0.38	1	6.40	0.16[a]
Pneumonia and bronchitis	480–486, 490, 491, 466	480–486, 490, 491, 466.0	3	2.90	1.03	1	1.79	0.56
Gastric and duodenal ulcer	531–533	531–533	0	0.32	0.00	0	0.17	0.00
Chronic liver diseases and cirrhosis	794	797	0	1.50	0.00	1	0.61	1.64
Nephritis, nephrose syndrome and nephrose	580–584	580–589	0	0.71	0.00	1	0.64	1.56
Accidents	E800–E949	E800–E949	3	2.29	1.31	0	0.80	0.00

[a]: $p < 0.05$

Unknown cause of death: male 5, female 8.

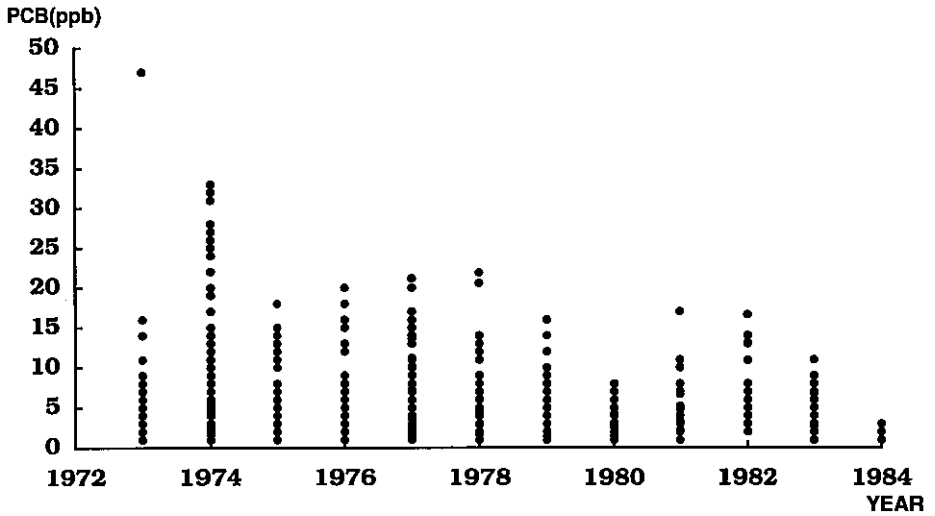

Fig. 10.1. The PCB Levels in the Serum of Yusho Patients and Year of Measurements

10.2. An Examination of the Association between Yusho Patients' Mortality and the PCB Levels and PCB Patterns

Among the patients with PCB data, the total number of deaths observed were 51, including 30 males and 21 females, as shown in Table 10.3. It was amazing that for both sexes, the deaths were significantly less than expected. As to be expected, such patients are more seriously concerned about their own health than the average non-affected persons. Such an attitude might have contributed to their lowered mortality, but no definite explanation can readily be made for the present findings.

It is quite important to examine whether the poisoning affects the mortality of the patients. In order to evaluate the possible effect of serum PCB levels and of gas chromatographic patterns of the PCBs (see chapter 4; Masuda, 1985) on mortality, we did a proportional hazard regression analysis for the cohort of patients' group with PCB data, using SAS procedure PHREG (SAS Institute Inc., 1988). As shown in Fig. 10.1, the serum PCB levels decreased according to the year of PCB measurement. A PCB level's regression line on the year of PCB measurement was calculated. The difference in the PCB levels from the regression line was defined as the adjusted PCB levels, where each PCB level was log-transformed. In the proportional hazard regression analysis, the survival length, which was a dependent variable, consisted of the duration of observation for each patient, while the PCB levels, PCB pattern A, PCB pattern B, age at the start of observation, and the year at each PCB measurement, were found to be independent variables. The age at the start of observation, and the year of the first PCB measurement were used as con-

Table 10.4. The Proportional Hazard Regression Analysis for Total Deaths (Male Patients with PCB Data)

Factor	Regression coefficiencies	Standard error	P value	Risk ratio
Age at start	0.072	0.014	0.0001	1.08
Year at start	0.051	0.089	0.5654	1.05
PCB pattern A	−1.035	0.471	0.0281	0.36[a]
PCB pattern B	−1.016	0.452	0.0244	0.36[a]
Adjusted PCB level[b]	0.833	0.629	0.1853	2.30

n = 407, [a]: as compared with the risk due to PCB pattern C, [b]: $\log_{10}$ (PCB level) − (−0.0148 Year + 1.377).

Table 10.5. The Proportional Hazard Regression Analysis for Total Deaths (Female Patients with PCB Data)

Factor	Regression coefficiencies	Standard error	P value	Risk ratio
Age at start	0.091	0.018	0.0001	1.10
Year at start	0.182	0.098	0.0644	1.20
PCB pattern A	−0.347	0.747	0.6423	0.71[a]
PCB pattern B	−0.058	0.510	0.9093	0.94[a]
Adjusted PCB level[b]	−0.769	0.996	0.4402	0.46

n = 458, [a]: as compared with the risk due to PCB pattern C, [b]: $\log_{10}$ (PCB level) − (−0.0148 Year + 1.377).

trolling factors for age and calendar year.

As shown in Tables 10.4 and 10.5, the total deaths increased as the PCB level increased in males, but decreased in females, and neither finding was significant. However, the relative risk of PCB pattern A for total deaths, as compared with the corresponding risk of PCB pattern C, was less than unity in males ($p < 0.05$). A similar decreased relative risk was also observed for PCB pattern B in males ($p < 0.05$). The relative risks of both type A and type B were less than unity in females, but did not demonstrate statistical significance.

In order to know whether the excess deaths from liver cancer are associated with the blood PCB levels or PCB patterns, a similar regression analysis was conducted. However, because of the small number of the liver cancer deaths (only three) we could not accurately evaluate such a possible relationship.

Although our cohort analysis (10.1) suggested that Yusho poisoning might have caused liver cancer, at least in male patients, it still seems to be too early to draw any conclusions on this issue, because we have not yet succeeded in showing any dose-response relationship between the mortality from liver cancer and the blood PCB levels and patterns. Needless to say, however, we must be particularly cau-

tious about the possible high risk of liver cancer in Yusho patients, because the tumorigenicity of PCBs and PCDFs to the liver of animals has been previously reported (Kimura and Baba, 1973; Nagasaki et al., 1972; Nishizumi, 1989)

References

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