A Longitudinal Analysis on the Association of Serum Lipidsand Lipoproteins Concentrations with Blood Polychlorinated Biphenyls Level in Chronic "Yusho" Patients

Tokunaga, Shoji
Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University

Kataoka, Kyoichiro
Fukuoka Institute of Health and Environmental Sciences

https://doi.org/10.15017/18744

出版情報：福岡醫學雜誌. 94 (5), pp.110-117, 2003-05-25. 福岡医学会
バージョン：
権利関係：

Fukuoka Acta Med. 94(5) : 110−117, 2003

A Longitudinal Analysis on the Association of Serum Lipids and Lipoproteins Concentrations with Blood Polychlorinated Biphenyls Level in Chronic "Yusho" Patients

Shoji TOKUNAGA

Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan

Kyoichiro KATAOKA

Fukuoka Institute of Health and Environmental Sciences, 39 Mukaizano, Dazaifu-shi, Fukuoka, 818-0135, Japan

Abstract We examined the association between blood PCB level and the serum concentrations of total cholesterol, high-density lipoprotein cholesterol and triglycerides. The data was retrieved from the dataset of the nationwide health examination for Yusho patients. We longitudinally analyze the laboratory data of the officially identified Yusho patients who underwent the health examination in Fukuoka and Nagasaki prefectures five times or more during the years from 1986 to 2000. For the longitudinal analysis, the generalized estimating equation model was used adjusting for the age as of 1986, the year of taking the health examination, smoking and drinking habits, body mass index and the site of the examination (Fukuoka or Nagasaki). Ten-fold increase in blood PCB level was associated with the elevation in serum concentration of total cholesterol by 18.4 mg/dL (95% CI, 7.8 to 29.0, $P<0.001$) in men and 19.7 mg/dL (95% CI, 8.3 to 31.2, $P<0.001$) in women, and the elevation of serum concentration of triglycerides by 43.4% (95% CI, 17.5 to 74.9, $P<0.001$) in men and 42.8% (95% CI, 25.7 to 62.1, $P<0.001$) in women. Association of blood PCB level with serum concentration of high-density lipoprotein cholesterol was not statistically significant in both men and women. Hypercholesterolemia is a well known risk factor of coronary heart disease. It might be suggested that the high blood PCB level in Yusho patients has some possible health effects on the incidence of coronary heart disease.

Introduction

"Yusho" is a poisoning caused by the ingestions of rice bran oil contaminated by polychlorinated biphenyls (PCB) and its related compounds, such as polychlorinated dibenzofurans (PCDF) and polychlorinated quarterphenyls (PCQ)[13]. The Yusho outbreak occurred in Western Japan in 1968[10]. Even 20 years after the outbreak, the average total PCB concentration in Yusho patients' blood were 4.9 times higher than that of the controls sampled from the general population[14]. For more than 20 years after the outbreak, there have been reports indicating the abnormality in the clinical data on the concentrations of triglycerides, thyroid stimulating hormone and immunoglobulins among Yusho patients[6][19][20]. Several cross-sectional studies showed statistically significant associations between blood PCB level and serum concentrations of triglycerides, total cholesterol and blood pressure[1][6][18]. These observed associations were based on the data taken by one-year basis, although the Yusho health examina-

tion has been conducted annually from 1986. In this study, we longitudinally analyze the data taken for 15 years. This is the first longitudinal analysis on the association of serum lipids and lipoproteins with blood PCB level.

Subjects and Methods

The data analyzed in the current study was retrieved from the database provided by the data-processing system of the nationwide health examination for Yusho patients established by Kataoka et al. (1989)[8]. The nationwide health examination for Yusho has been conducted annually from 1986 to promote the health of the patients and determine the health status of the chronic Yusho patients[7]. The examination is open not only to officially identified Yusho patients, but also to those who regard themselves as potential victims. The participation to the examination is voluntary. The examination is comprehensive and the dataset includes demographic and laboratory data and the data on the manifestations of symptoms[7]. The examination was conducted at each prefecture. Serum concentrations of total cholesterol, high-density lipoprotein cholesterol and triglycerides of the residents in Fukuoka and Nagasaki prefectures were measured at the same laboratory. Blood polychlorinated biphenyls (PCB) level was analyzed at each prefecture where the health examination was conducted.

The data from 1986 to 2000 was available for the current analysis. Eligible observations for the analysis were 1) those of officially identified Yusho patients, 2) those without missing values in any of blood PCB level, serum concentrations of total cholesterol, high-density lipoprotein cholesterol and triglycerides, smoking and drinking habits, height and weight, 3) those of the patients who underwent the health examination at Fukuoka or Nagasaki prefecture where the Yusho outbreaks were most prominent, and 4) those of the patients with the number of observations satisfying the conditions of 1) through 3) was five or more.

Mean and standard deviation were calculated to show the summary statistics except for blood PCB level and serum concentration of triglycerides. Geometric mean and 90% central range were calculated as their summary statistics, because their distributions were highly skewed to the right. For the longitudinal data analysis, the generalized estimating equation (GEE) model was applied. The observations for a particular individual in the database were not independent; therefore, a within-patient correlation structure was specified. The linear regression model was created with an equal within-patient correlations structure, i.e., the correlations between each year within the same patient were assumed to be equal. In addition, we implemented the Huber/White/Sandwich estimator of variance that yields valid standard error estimation even if the within-patient correlations are not as hypothesized[16]. By the GEE model, the association of the serum concentrations of total cholesterol, high-density lipoprotein cholesterol and $\log_{10}$ (triglycerides) with $\log_{10}$ (blood PCB level) was analyzed adjusting for the age as of 1986, the year of taking the health examination, smoking habit (current smoker or not), drinking habit (current drinker or not), body mass index (body weight divided by height^2) and the site of the examination (Fukuoka or Nagasaki). Statistical analyses were performed with the statistical package Stata ver. 7.0[16]. All the statistical tests were two-sided and the significance level was set to 0.05.

Table 1 The demographic data of the subjects.

	Site of health examination		
	Fukuoka	Nagasaki	Total
Number of subjects	117	107	224
Sex (% men)	46.2	37.4	42.0
Mean age as of 1986 (SD)	56.3 (9.95)	54.0 (12.72)	55.2 (11.39)
Mean number of observations per subject (SD)	9.3 (3.15)	9.4 (3.03)	9.3 (3.08)

Results

The demographic data was shown in Table 1. Fifty two percent of the subjects underwent the health examination at Fukuoka. The numbers of eligible male and female subjects were 54 and 63, respectively, in Fukuoka and 40 and 67, respectively, in Nagasaki. The difference in sex ratio between the sites of examination was not statistically significant. Mean age of the eligible subjects was 55 at the first year of the study period. Mean number of examinations that the subjects had undergone during the study period was 9.3.

The summary statistics of the blood polychlorinated biphenyls (PCB) level and serum concentrations of serum lipids and lipoproteins were shown in Table 2a and 2b. Number of eligible observations in a year ranged from 43 to 67 in men and from 66 to 98 in women. In total, number of observations eligible for the analysis was 844 in men and 1240 in women. Blood PCB level

Table 2a Summary statistics of blood PCB level and serum concentrations of total cholesterol, high-density lipoprotein cholesterol and triglycerides by the year of health examination in men.

			Serum concentration (mg/dL)		
Year	Number of observations	Blood PCB level (ppb)	Total cholesterol	High-density lipoprotein cholesterol	Triglycerides
1986	43	5.83 (2.6 to 14.0)*	191 (28.5)†	49 (10.1) †	111 (49 to 323)*
1987	51	4.49 (2.0 to 15.0)	198 (34.7)	48 (10.5)	109 (57 to 276)
1988	55	4.85 (1.4 to 13.0)	204 (41.4)	47 (9.6)	118 (58 to 363)
1989	52	4.34 (1.2 to 10.0)	198 (41.2)	46 (9.5)	108 (51 to 371)
1990	65	4.07 (1.1 to 10.8)	195 (36.6)	50 (11.0)	102 (51 to 251)
1991	54	4.45 (1.3 to 11.0)	192 (26.4)	50 (10.3)	90 (52 to 373)
1992	56	3.48 (1.0 to 9.4)	201 (26.7)	51 (13.8)	100 (46 to 301)
1993	65	4.88 (1.9 to 11.0)	196 (33.5)	53 (14.2)	96 (48 to 222)
1994	67	3.87 (1.0 to 9.0)	186 (33.3)	50 (13.8)	101 (47 to 220)
1995	56	3.39 (0.9 to 7.0)	197 (34.1)	49 (15.3)	97 (49 to 311)
1996	58	3.28 (1.0 to 10.0)	194 (33.3)	50 (12.8)	101 (51 to 276)
1997	58	2.99 (1.1 to 8.0)	207 (32.2)	54 (13.3)	102 (42 to 297)
1998	61	2.90 (0.8 to 8.0)	202 (32.9)	53 (11.3)	107 (47 to 251)
1999	53	3.01 (1.0 to 8.0)	204 (35.7)	53 (10.0)	98 (44 to 278)
2000	50	2.86 (1.0 to 8.0)	199 (35.8)	51 (10.2)	103 (48 to 259)
Total	844	3.80 (1.0 to 10.0)	198 (34.2)	50 (12.1)	102 (49 to 276)

* : Geometric mean (90% central range).
† : Mean (SD).

Table 2b Summary statistics of blood PCB level and serum concentrations of total cholesterol, high-density lipoprotein cholesterol and triglycerides by the year of health examination in women.

Year	Number of observations	Blood PCB level (ppb)	Serum concentration (mg/dL) Total cholesterol	High-density lipoprotein cholesterol	Triglycerides
1986	78	4.12 (1.0 to 12.0)*	209 (47.1)†	54 (11.6) †	98 (38 to 269)*
1987	66	4.31 (1.5 to 11.0)	216 (42.5)	49 (10.1)	106 (48 to 241)
1988	77	4.07 (1.5 to 8.0)	216 (41.8)	52 (12.3)	101 (52 to 243)
1989	85	3.86 (1.4 to 11.7)	213 (40.2)	51 (10.1)	110 (52 to 253)
1990	98	3.96 (1.2 to 11.3)	220 (42.4)	52 (10.3)	93 (48 to 200)
1991	79	3.92 (1.5 to 13.0)	212 (34.2)	55 (12.2)	93 (44 to 207)
1992	86	3.66 (1.5 to 10.1)	214 (36.0)	55 (12.0)	95 (44 to 211)
1993	96	4.03 (1.7 to 10.7)	211 (32.4)	55 (11.8)	92 (45 to 205)
1994	92	3.69 (1.6 to 9.0)	207 (35.0)	54 (13.4)	94 (44 to 200)
1995	88	3.21 (1.3 to 8.6)	211 (32.2)	54 (13.0)	92 (44 to 170)
1996	83	3.13 (1.1 to 8.2)	212 (39.2)	56 (12.8)	97 (51 to 187)
1997	80	2.71 (1.0 to 6.2)	221 (38.4)	60 (15.8)	97 (47 to 220)
1998	80	2.85 (1.0 to 12.6)	211 (34.0)	59 (13.4)	96 (46 to 200)
1999	73	3.06 (1.0 to 7.1)	224 (38.4)	63 (14.0)	96 (45 to 257)
2000	79	2.96 (1.0 to 8.0)	209 (35.1)	60 (16.0)	92 (42 to 222)
Total	1240	3.54 (1.1 to 9.2)	214 (38.1)	55 (13.1)	97 (46 to 216)

* : Geometric mean (90% central range).
† : Mean (SD).

showed large variation. The difference between 5 percentile and 95 percentile of the PCB level in each year was more than five-fold and reached to twelve-fold. During the study period, geometric mean of blood PCB level (ppb) gradually decreased from 5.83 to 2.86 in men and from 4.12 to 2.96 in women. Mean serum concentrations of lipids and lipoproteins in men and women, however, changed little and showed no particular time trend.

The results of the longitudinal analysis on the associations between blood PCB level and serum concentrations of lipids and lipoproteins were shown in Table 3. Ten-fold rise in blood PCB level was associated with the elevation in serum concentration of total cholesterol by 18.4 (95% confidence

Table 3 The association of blood PCB level with serum concentrations of total cholesterol, high-density lipoprotein cholesterol and triglycerides.

Response variable (unit)	Men β*(95% confidence interval)	P	Women β*(95% confidence interval)	P
Total cholesterol (mg/dL)	18.4 (7.8 to 29.0)†	<0.001	19.7 (8.3 to 31.2)†	<0.001
High-density lipoprotein cholesterol (mg/dL)	0.6 (-4.2 to 5.5)†	0.79	-2.9 (-6.1 to 0.4)†	0.09
Triglycerides (%)	43.4 (17.5 to 74.9)‡	<0.001	42.8 (25.7 to 62.1)‡	<0.001

* Regression coefficient for $\log_{10}$-transformed blood PCB level.
† Estimated increase of the response variable with 10-fold increase in blood PCB level.
‡ Estimated increase of the response variable expressed in percent with 10-fold increase in blood PCB level.

interval, 7.8 to 29.0) mg/dL in men and 19.7 (95% confidence interval, 8.3 to 31.2) mg/dL in women. The association was statistically significant with the significance level of less than 0.001 for both sexes. Ten-fold rise in blood PCB level was associated with the elevation of serum concentration of triglycerides by 43.4 (95% confidence interval, 17.5 to 74.9) % in men and 42.8 (95% confidence interval, 25.7 to 62.1) % in women. The observed elevation was statistically significant ($P<0.001$) both in men and women. Association of blood PCB level with serum concentration of high-density lipoprotein cholesterol was not statistically significant in both men and women.

Discussion

The present study analyzed the longitudinal data consisting of 2084 observations of 224 Yusho patients who have undergone annual health examination during the years from 1986 to 2000. From the dataset, we observed positive and statistically significant associations of blood PCB level with serum concentrations of total cholesterol and triglycerides in men and women. Ten-fold increase in blood PCB level was associated with the elevation of serum concentration of total cholesterol by about 19 mg/dL, and the elevation of serum concentration of triglycerides by 43 %. For high-density lipoprotein cholesterol, we could not observe the statistically significant association with blood PCB level.

The results of the present study support the findings from the former studies on the association of blood polychlorinated biphenyls (PCB) level and the serum concentrations of triglycerides[5)6)15)18)21)] and total cholesterol[18)] observed by cross-sectional analyses on the one-year based data of Yusho patients. The present study was different from the former studies in that the data spanning at least five up to fifteen years were analyzed longitudinally. The longitudinal study design is supposed to be superior to the one-year based cross-sectional study design, which can be more prone to be affected by a sampling bias of the subjects and the measurement error of the clinical data. Therefore, it is suggested that the current study presents more reliable evidence on the associations between blood PCB level and the serum concentrations of triglycerides and total cholesterol.

The current study has limitations common to most other observational studies in that the observed association does not always mean the causal relationship. Thus, the interpretation of the results should be careful. In the current study, the observations from the subjects who had taken the Yusho health examination 5 times or more were analyzed. The small number of subjects who were eligible for the study might cause selection bias of the subjects. To examine this possibility, we changed the criterion on the times of health examinations taken by a patient from 4 to 7, and the results of the analyses were compared. Under the different criteria for the selection of the subjects, the statistical significance of the association was held and the estimated relationship was stable. Therefore, it is difficult to explain the observed associations by selection bias only. Another limitation of the current analysis is that the data of possible confounding factors such as dietary habits and the use of antilipidemic agents were not available for the analysis. In spite of the above limitations, the observed associations of serum concentrations of triglycerides and total cholesterol with blood PCB level paralleled with the results of other studies on non-Yusho patients[9)17)].

Hence, the observed association in Yusho patients might hold in the general population exposed to high level of PCB. Further analyses are needed to establish the association of the blood PCB level with the serum lipids and lipoproteins concentrations, in particular, the serum concentration of total cholesterol.

Hypercholesterolemia is a well known risk factor of the incidence of coronary heart disease[3)4)12)]. Cohort study estimate shows that the increase in serum cholesterol concentration by 10% was associated with an increase in incidence of ischaemic heart disease of 27% in Western countries[11)]. A 4% difference in usual cholesterol concentration was associated with a 21% difference in mortality from coronary heart disease in a Chinese population[4)]. High levels of serum triglycerides when accompanied by low high-density lipoprotein cholesterolemia are shown to represent increased risk of coronary heart disease[2)]. The observed association of hypercholesterolemia and elevated triglycerides concentration with blood PCB level may suggest the higher risk of coronary heart disease of Yusho patients, particularly those with very high PCB level. Each year, the ratio of 95 percentile to 5 percentile of blood PCB level was about 10 (Table 2a and 2b), and ten-fold increase in blood PCB level was associated with the elevation of serum total cholesterol concentration by 9% of the mean concentration. Therefore, the results of the present study can be translated that the ten-fold difference observed in the blood PCB level of Yusho patients is estimated to the difference in the incidence or mortality of coronary heart disease by 24 to 47%. It might be suggested that the high blood PCB level in Yusho patients has some possible health effects on the incidence of coronary heart disease.

References

1) Akagi K and Okumura M : Association of blood pressure and PCB level in yusho patients. Environ Health Perspect. 59 : 37- 39, 1985.
2) Assmann G, Betteridge DJ, Gotto AM, Jr and Steiner G : Management of hypertriglyceridemic patients. A. Treatment classifications and goals. Am J Cardiol. 68 : 30A-34A, 1991.
3) Castelli WP : Epidemiology of coronary heart disease : the Framingham study. Am J Med. 76 : 4-12, 1984.
4) Chen Z, Peto R, Collins R, MacMahon S, Lu J and Li W : Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ. 303 : 276-282, 1991.
5) Hirota Y, Hirohata T, Kataoka K, Shinohara S and Tokiwa H : Laboratory findings in the medical examination of chronic "Yusho" (PCB poisoning) patients : with special reference to blood PCB and serum triglyceride. Fukuoka Acta Med. 84 : 287-293, 1993. (in Japanese)
6) Hirota Y, Kataoka K, Tokunaga S, Hirohata T, Shinohara S and Tokiwa H : Association between blood polychlorinated biphenyl concentration and serum triglyceride level in chronic "Yusho" (polychlorinated biphenyl poisoning) patients. Int Arch Occup Environ Health. 65 : 221-225, 1993.
7) Hirota Y, Kataoka K and Hirohata T : Annual health examination of Yusho patients. In Kuratsune M, Yoshimura H, Hori Y, Okumura M, Masuda Y, (eds) : YUSHO - A human disaster caused by PCBs and related compounds. pp. 249-266, Kyushu University Press, Fukuoka, 1996.
8) Kataoka K, Okubo A and Shinohara S : Introduction of the information processing system of medical examinations of Yusho patients and some results obtained by the survey. Fukuoka Acta Med. 80 : 331-341 1989. (in Japanese)
9) Kreiss K, Zack MM, Kimbrough RD, Needham LL, Smrek AL and Jones BT : Association of blood pressure and polych-

lorinated biphenyl levels. JAMA. 245: 2505-2509, 1981.
10) Kuratsune M, Yoshimura H, Hori Y, Okumura M and Masuda Y: YUSHO - A human disaster caused by PCBs and related compounds. Kyushu University Press, Fukuoka, 1996.
11) Law MR, Wald NJ and Thompson SG: By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ. 308: 367-372, 1994.
12) Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH and Harlan WR: Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. Ann Epidemiol. 2: 161-176, 1992.
13) Masuda Y: Causal agents of Yusho. In Kuratsune M, Yoshimura H, Hori Y, Okumura M, Masuda Y, (eds): YUSHO - A human disaster caused by PCBs and related compounds. pp. 49-80, Kyushu University Press, Fukuoka, 1996.
14) Masuda Y, Kuroki H, Haraguchi K, Schecter A and Papke O: The condition of PCBs and PCDFs in the blood of Yusho patients 20 years after the onset. Fukuoka Acta Med. 88: 149-156, 1997. (in Japanese)
15) Okumura M, Masuda Y and Nakamuta S: Correlation between blood PCB and serum triglyceride levels in patients with PCB poisoning. Fukuoka Acta Med. 65: 84-87, 1974. (in Japanese)
16) StataCorp. Stata Statistical Software: Release 7.0. Stata Press, College Stataion, Texas, 2001.
17) Stehr-Green PA, Welty E, Steele G and Steinberg K: Evaluation of potential health effects associated with serum polychlorinated biphenyl levels. Environ Health Perspect. 70: 255-259, 1986.
18) Tokunaga S, Hirota Y and Kataoka K: Association between the results of blood test and blood PCB level of chronic Yusho patients twenty five years after the outbreak. Fukuoka Acta Med. 90: 157-161, 1999. (in Japanese)
19) Tsuji H, Sato K, Shimono J, Azuma K, Hashiguchi M and Fujishima M: Thyroid function in patients with Yusho: 28 year follow-up study. Fukuoka Acta Med. 88: 231-235, 1997. (in Japanese)
20) Tsuji H, Hirahashi T, Ogata H and Fujishima M: Serum immunoglobulin concentrations and autoantibodies in patients with Yusho. Fukuoka Acta Med. 90: 147-149, 1999. (in Japanese)
21) Uzawa H, Ito Y, Notomi A and Katsuki S: Hyperglyceridemia resulting from intake of rice oil contaminated with chlorinated biphenyls. Fukuoka Acta Med. 60: 449-454, 1969. (in Japanese)

(Received for publication March 24, 2003)

(和文抄録)

油症患者の経時的繰り返し測定データの統計学的解析による血清脂質及びリポタンパクと血中PCB濃度の関連

九州大学大学院医学研究院予防医学分野
徳永章二
福岡県保健環境研究所
片岡恭一郎

1986年から2000年までの15年間の全国油症患者追跡検診結果をもとに，福岡県と長崎県で観察期間中5回以上受診した認定患者について，経時的に繰り返し測定された血中ＰＣＢ濃度と総コレステロール，HDL-コレステロール，及び，中性脂肪の血清濃度との関連を統計学的に吟味した．解析には一般化推定方程式（Generalized Estimating Equation）モデルを用い，1986年現在の年齢，受診年度，飲酒・喫煙習慣，BMI（体重/身長^2），受診地で統計学的に調整した．その結果，血中PCB濃度が10倍になると血清総コレステロール濃度が男性で18.4 mg/dL（95%信頼区間，7.8-29.0，P<0.001），女性で19.7 mg/dL（95%信頼区間，8.3 - 31.2，P<0.001）上昇し，血清中性脂肪濃度が男性で43.4%（95%信頼区間，17.5 - 74.9，P<0.001），女性で42.8%(95%信頼区間，25.7-62.1，P<0.001)上昇すると推定された．血清HDL-コレステロール濃度と血中PCB濃度との間には統計学的に有意な関連は見いだされなかった．血清総コレステロール濃度の上昇が冠動脈疾患のリスク要因であることは良く知られている．油症患者に見られる高い血中PCB濃度を考慮すると，少なくとも一部の油症患者の冠動脈疾患罹患に対して影響が及ぼされている可能性が示唆された．