IS TYPE 2 DIABETES MELLITUS RISK INCREASED AMONG YUCHENG COHORT? – A 24-YEAR FOLLOW-UP STUDY

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Abstract
There has been debate on causal association between type 2 diabetes and dioxins and polychlorinated biphenyls. Current report of 24-year follow-up of Yucheng cohort may provide a good opportunity for the hypothesis examination. The matched controls recruited based on registered 2,061 exposed cases during 1979-93. Between 1993 and 2003, we have followed 1144 exposed subjects and their controls by trained interviewers blinded to exposure status. For the current study, individually well paired 506 Yucheng subjects and their matched controls were reported. Odds ratio of diabetes for Yucheng relative to controls remained significant (OR=3.4, 95% CI: 1.2-11.3) for 55-64 age group, after the adjustment for age, BMI, cigarette smoking and alcohol drinking. We compared diabetes rate in subjects with chloracne to those without, and found highly significant Adjusted OR of 5.2 (2.1-14.1) in women but not in men. We report increased type 2 diabetes risk associated with PCBs/PCDFs body burden in Yucheng women at the age between 55 and 64 years in 2003, particularly among those with chloracne. Reason for the higher risk for women needs further investigations. The mechanisms may involve estrogen dependent PPAR pathway leading to down-regulation of IGFBP-1 and/or IRS-1.

Introduction
There has been debate on causal association between type 2 diabetes occurrence and body burden of persistent organic pollutants; particularly with dioxins and polychlorinated biphenyls (PCBs)[1,2]. Current report of 24-year follow-up of Yucheng cohort may provide a good opportunity for the hypothesis examination. In 1979, over 2000 people in central Taiwan ingested cooking rice oil contaminated with polychlorinated biphenyls (PCBs) and dibenzo-furans (PCDFs), with 10-40 times higher than background and 10,000 times higher for penta-CDF[3]. This report focused on individuals born before 1 January 196 for subjects all over the age of 40 years, in order to study the chronic disease of type 2 diabetes risks.

Materials and Methods
From 1979 to 1983 the Taiwan Provincial Department of Health registered 2,061 cases based on signs and symptoms of the illness or a history of consumption of the contaminated oil. Participation in the registry was voluntary, and the registration provided free access examinations and medical care. The individual matched controls recruited in 1993 were from the neighborhood with the same gender, within 3 years of age and not in the registry. Between 1993 and 2003, we have carried out morbidity follow-up of 1144 exposed subjects and their controls by trained interviewers blinded to exposure status. The information on disease diagnosed or treated by western-style medical doctors was acquired by phone. For the current study, individually well paired 506 Yucheng subjects and their matched controls were reported.
The serum samples collected in 1979-83 were analyzed for total PCBs by means of packed-column, electron-capture gas chromatography and an adaptation of the Webb-McCall method to a computer data system, in which PCBs (Kanechlor 500) were used as reference standard. Student t and Chi-square tests was used to compare continuous and categorical variables between the exposed and control groups. Univarient and multivarient logistic regression models were utilized to evaluate odds ratios for diabetes prevalence among exposed relative to control subjects with or without adjustment for potential covariates.

Results and Discussion
Table 1 shows very similar distribution in age, gender body mass index (BMI), education, life style and occupational between Yucheng cohort and their age and gender matched controls. Mean PCBs in Yucheng subjects, with large variation, were about 40-50 folds of controls.
Diabetes risk increased substantially in 55-64 age group particularly for women (Table 2). Odds ratio of diabetes

for Yucheng relative to controls remained significant (OR=3.4, 95% CI: 1.2-11.3) after the adjustment for age, BMI, cigarette smoking and alcohol drinking. Physical activity and diet habits were not detailed recoded during the interview. However, we believe that it would be different substantially because social-economic status was also very similar between the two groups. The prevalence of diabetes in controls (7.8%) was comparative to the ones in the national survey in Taiwan[5]. The 55-64 age group has a mean age of about 60 years. Thus the Yucheng subjects might be heavily exposed at the mean ages of around 35 years. It might be suggested that the excess risk of diabetes may occur after the incidental exposure to PCBs/PCDFs. Other related chronic diseases such as hypertension, cardiovascular diseases, endometriosis and hormonal abnormality also have increased ORs but without statistical significance. Yucheng subjects experienced very high risk of having chloracne as compared to the controls with Adjusted OR of about 40. The exposure was based self-report to get registered and free medical examinations and care. We suspected that there might be some misclassification from control to exposure group in which case the ORs might be underestimated.

We compared diabetes rate in subjects with chloracne to those without, and found highly significant AOR of 5.2 in women but not in men (Table 3). This is also true for hypertension, cardiovascular disease and hypothyroidism. It is interesting that women with chloracne did not have significantly higher PCBs than those without (114 vs. 81 ppb, p=0.1). This might resulted from limited sample size or some common genetic susceptibility for diabetes/hypertension to chloracne in women. On the other hand, one may think of females being more vulnerable to PCBs/PCDFs intoxication than men. Further studies are warrant for this gender difference.
Tetra-chlorinated dibenzo-p-dioxin (TCDD) was found up-regulate Insulin-like Growth Factor Biding Protein-1 (IGFBP-1)[6] in MCF-7 cells co-treating estrogens by most likely Peroxisome proliferator-activated receptor (PPAR) pathway[7], and also in female AhR knockout female rats[8]. This counterpart insulin action which down-regulates IGFBP-1. Thus dioxin may disrupt glucose homeostasis. In addition, TCDD-altered insulin receptor substrate-1 (IRS-1) down-regulation was reported in MCF-7 cells[8]. These may confer to our observation and might explain in pat the etiology of dioxin-like chemicals causing type 2 diabetes. This situation might be exaggerated as a result from hypertriglycemia state usually in diabetic patients and thus delay the degradation and/or excretion of the lipophilic compounds.

Table 1. General characteristics in Yucheng cohort and their matched controls in 2003

Characteristics	men			women		
	Yucheng (n=174)	Control (n=174)	p	Yucheng (n=332)	Control (n=332)	p
Age (years, %)	59.5±12.1[a]	59.1±12.0	ns	48.6±12.9	48.4±12.8	ns
<45	28 (16.1)	28 (16.1)		158 (47.6)	158 (47.6)	
45-54	41 (23.6)	41 (23.6)		86 (25.9)	90 (27.1)	
55-64	40 (22.9)	44 (25.3)		38 (11.5)	33 (9.9)	
≥65	65 (37.4)	61 (35.0)		50 (15.0)	51 (15.4)	
BMI (kg/m^2)	24.2±3.0	24.0±3.1	ns	23.9±7.5	23.2±3.4	ns
Education (years)	7.3±4.2	7.0±3.8	ns	7.6±4.7	8.0±4.6	ns
Current smoker (%)	92 (53.5)[b]	105 (61.8)	ns	4 (1.2)	1 (0.3)	ns
Alcohol Drinking (%)	46 (27.1)	39 (23.1)	ns	5 (1.3)	2 (0.6)	ns
Occupation (%):						
None	77 (44.3)	72 (41.3)	ns	149 (44.9)	137 (41.3)	ns
Government	6 (3.5)	4 (2.3)		16 (4.8)	17 (5.0)	
Agriculture	13 (7.5)	24 (13.8)		6 (1.8)	8 (2.4)	
Manufacturing	61 (35.1)	60 (34.5)		119 (35.8)	122 (36.8)	
Commercial	18 (9.6)	14 (8.1)		42 (12.7)	48 (14.5)	
Serum PCBs (ppb)	71.6±79.9	1.67		89.0±135.4	1.67	

a. Mean±standard deviation.
b. Values shown in parentheses are percent.
c. General population had mean serum PCB levels of 1.67 ppb wet weight as previously reported[4]

Table 2. Prevalence (%) of reported diseases ever diagnosed by a physician in Yucheng and control groups by gender in Taiwan, 2003

	Men				women				total			
	Yucheng (n=174)	Control (n=174)	OR (95% CI)	AOR	Yucheng (n=332)	Control (n=332)	OR (95% CI)	AOR	Yucheng (n=506)	Control (n=506)	OR (95% CI)	AOR
Chloracne	75 (43.6)	1 (0.6)	130.7 *** (28.3-2322)	125.1*** (26.7-2233.7)	82 (24.9)	4 (1.2)	26.5 *** (10.9-87.7)	23.4 *** (9.6-77.7)	157 (31.3)	5 (1.0)	44.6 * (20.1-126.6)	39.7 *** (17.8-113.0)
Type 2 Diabetes	23 (13.5)	24 (14.1)	0.9 (0.5-1.8)	0.9 (0.5-1.8)	25 (7.6)	20 (6.1)	1.2 (0.7-2.3)	2.2 * (1.0-4.7)	48 (9.6)	44 (8.9)	1.1 (0.7-1.7)	1.3 (0.8-2.1)
<55	3 (4.4)	7 (10.5)	0.4 (0.1-1.5)	0.5 (0.1-2.0)	7 (2.9)	7 (2.9)	1.0 (0.3-3.0)	1.0 (0.3-3.1)	10 (3.2)	14 (4.5)	0.7 (0.3-1.6)	0.7 (0.3-1.6)
55-64	9 (23.1)	5 (11.4)	2.3 (0.7-8.3)	3.7 (0.9-17.6)	6 (15.8)	1 (3.0)	6.0* (1.0-117)	-	15 (19.5)	6 (7.8)	2.9* (1.1-8.4)	3.4 * (1.2-11.3)
≥65	11 (17.5)	12 (20.3)	0.8 (0.3-2.1)	0.7 (0.3-2.1)	12 (24.5)	12 (23.5)	1.1 (0.4-2.7)	2.6 (0.9-9.3)	23 (20.5)	24 (21.8)	0.9 (0.5-1.8)	1.3 (0.6-2.9)
-on therapy	23 (13.4)	19 (11.2)	1.2 (0.6-2.4)	1.2 (0.6-2.5)	17 (5.2)	14 (4.3)	1.2 (0.6-2.5)	2.5 (1.0-6.7)	40 (8.0)	33 (6.7)	1.2 (0.8-2.0)	1.5 (0.9-2.7)
<55	3 (4.4)	3 (4.5)	1.0 (0.2-5.4)	1.2 (0.2-7.2)	3 (1.2)	5 (2.1)	0.6 (0.1-2.4)	0.6 (0.1-2.4)	6 (1.9)	8 (2.6)	0.7 (0.2-2.1)	0.8 (0.3-2.4)
55-64	9 (23.1)	5 (11.4)	2.3 (0.7-8.3)	3.7 (0.9-17.7)	3 (7.9)	0 (0.0)	-	-	12 (15.6)	5 (6.5)	2.7 (0.9-8.7)	2.7 (0.9-9.7)
≥65	11 (17.2)	11 (18.6)	0.9 (0.4-2.3)	0.9 (0.3-2.6)	11 (22.5)	9 (17.7)	1.4 (0.5-3.7)	6.6 * (1.6-45.4)	22 (19.5)	20 (18.2)	1.1 (0.6-2.1)	1.8 (0.8-4.1)
Gout	35 (20.4)	27 (15.9)	1.4 (0.8-2.4)	1.3 (0.7-2.4)	16 (4.9)	6 (1.8)	2.7* (1.1-7.7)	2.5* (1.0-7.4)	51 (10.2)	33 (6.7)	1.6 (1.0-2.5)	1.6* (1.0-2.6)
Hypo-Thyroidism	2 (1.2)	1 (0.6)	2.0 (0.2-43.2)	1.8 (0.2-39.5)	9 (2.7)	3 (0.9)	3.0 (0.9-13.7)	3.0 (0.9-13.6)	11 (2.2)	4 (0.8)	2.8 (0.9-10.0)	2.7 (0.9-10.0)
Goiter	0 (0.0)	0 (0.0)	-	-	19 (5.8)	5 (1.5)	3.9 ** (1.6-11.9)	3.9 ** (1.5-11.9)	19 (3.8)	5 (1.0)	3.9 ** (1.5-11.7)	3.9 ** (1.5-11.8)
-on therapy	0 (0.0)	0 (0.0)	-	-	15 (4.6)	5 (1.5)	3.1 ** (1.2-9.6)	3.0 ** (1.1-9.4)	15 (3.0)	5 (1.0)	3.1 ** (1.2-9.5)	3.0 ** (1.1-9.3)
Hypertension	53 (30.8)	45 (26.5)	1.2 (0.8-2.0)	1.1 (0.6-2.0)	50 (15.2)	41 (12.6)	1.2 (0.8-1.9)	1.2 (0.7-2.1)	103 (20.5)	86 (17.3)	1.2 (0.9-1.7)	1.1 (0.8-1.7)
-on therapy	47 (27.3)	35 (20.6)	1.5 (0.9-2.4)	1.3 (0.7-2.5)	35 (10.6)	28 (8.6)	1.3 (0.8-2.1)	1.4 (0.7-2.6)	82 (16.3)	63 (12.7)	1.3 (0.9-1.9)	1.3 (0.8-2.0)
CVD	26 (15.0)	17 (9.8)	1.6 (0.9-3.2)	1.2 (0.6-2.5)	42 (12.7)	30 (9.0)	1.5 (0.9-2.4)	1.4 (0.8-2.5)	68 (13.4)	47 (9.3)	1.5 (1.0-2.3)	1.4 (0.9-2.1)
Endometriosis					6 (1.8)	2 (0.6)	3.0 (0.7-20.7)	3.2 (0.7-21.9)				

*: p <0.05, **: p <0.05, ***: p <0.001

AOR: Adjusted for age, BMI, cigarette smoking and alcohol drinking

Table 3. Lifetime prevalence of medical conditions (%) in Yucheng individuals without (-) or with (+) reported chloracne

	Men					Women				
	- (n=97)	+ (n=75)	p	OR	AOR	- (n=248)	+ (n=82)	P	OR	AOR
Age (mean±SD)	60.6±1.2	57.7±1.4	0.1			48.0±0.8	50.1±1.4	0.2		
BMI (mean±SD)	24.2±0.3	24.2±0.4	1.0			23.9±0.5	24.1±0.9	0.8		
Diabetes (%)	11 (11.3)	12 (16.2)	0.4	1.5 (0.6-3.7)	2.0 (0.7-5.5)	11 (4.4)	14 (17.1)	0.0005	4.4 *** (1.9-10.4)	5.2 *** (2.1-14.1)
Max. glucose (mean±SD)	274±34	220±39	0.3 (n=7)			232±24	275±38	0.4 (n=4)		
Hypertension (%)	34 (35.1)	19 (25.3)	0.2	0.6 (0.3-1.2)	0.7 (0.3-1.5)	28 (11.3)	22 (26.8)	0.0012	2.9 *** (1.5-5.4)	2.8 *** (1.3-6.2)
Hypothyroidism (%)	0 (0.0)	2 (2.7)	0.1	-	-	4 (1.6)	5 (6.1)	0.05	4.0 * (1.0-16.3)	4.3 * (1.1-18.0)
Goiter (%)	0 (0.0)	0 (0.0)	--	-	-	11 (4.4)	8 (9.8)	0.09	2.3 (0.9-6.0)	2.3 (0.9-6.1)
Gout (%)	20 (20.6)	15 (20.0)	0.9	1.0 (0.4-2.0)	1.0 (0.4-2.2)	10 (4.0)	6 (7.3)	0.3	1.9 (0.6-5.2)	2.0 (0.6-5.9)
CVD (%)	14 (14.4)	12 (16.0)	0.8	1.1 (0.5-2.6)	1.0 (0.4-2.7)	25 (10.1)	17 (20.7)	0.02	2.3 * (1.2-4.6)	2.6 * (1.2-5.5)
PCB (ppb) (mean±SD)	53.9±9.2	95.8±10.1	0.003			81.0±10.6	113.7±17.4	0.11		

*: p <0.05, **: p <0.05, ***: p <0.001
AOR: Adjusted odds ratio for age, BMI, cigarette smoking and alcohol drinking

In conclusion, increased type 2 diabetes was associated with PCBs/PCDFs body burden in Yucheng women at the ages between 55 and 64 in 2003, particularly among those with reported chloracne. The disease is likely to occur after the incidentally exposure to high PCBs/PCDFs. It is suggested that this causal factor might increase diabetes risk through estrogen dependent PPAR pathway leading to down-regulation of IGFBP-1 and/or IRS-1.

References

1. Everett CJ, Frithsen IL, Diaz VA, Koopman RJ, Simpson WM Jr, Mainous AG. *Environ Res* 2007; 103:413.
2. Longnecker MP, Daniels JL. *Environ Health Perspect* 2001; 109 (S6):871.
3. Svensson BG, Nilsson A, Hansson M, Rappe C, Akesson B, Skerfving S. *N Engl J Med* 1991; 324:8.
4. Guo YL, Ryan JJ, Lau BP, Yu ML, Hsu CC. *Arch Environ Contam Toxicol* 1997; 33:104-8.
5. Pan WH, Yeh WT, Chang HY, Hwu CM, Ho LT. *Diabet Med* 2003; 20:182. .
6. Marchand A, Tomkiewicz C, Marchandeau JP, Boitier E, Barouki RM. *Mol Pharmaco* 2005; 67:444.
7. Kuwabara K, Murakami K, Todo M, Aoki T, Asaki T, Murai M, Yano J. *J Pharmacol Exp Ther* 2004; 309:970.
8. Lind PM, Orberg J, Edlund UB, Sjoblom L, Lind L. *Toxicol Lett* 2004;150:293.
9. Hokanson R, Miller S, Hennessey M, Flesher M, Hanneman W, Bush. *Hum Exp Toxicol* 2004; 23:555.