Increased Risk of Diabetes and Polychlorinated Biphenyls and Dioxins

A 24-year follow-up study of the Yucheng cohort

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OBJECTIVE — Polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) are important and persistent organic pollutants (POPs) in humans. Recent cross-sectional studies have detected increased concentrations of serum POPs in diabetic patients. We aimed to examine the association between previous high exposures to PCBs and PCDFs and the cumulative incidence of type 2 diabetes and hypertension.

RESEARCH DESIGN AND METHODS — During the late 1970s, the consumption of rice-bran oil laced with PCBs poisoned thousands of Taiwanese. Between 1993 and 2003, we examined 1,054 Yucheng ("oil disease") victims against neighborhood reference subjects using a protocol blinded for POP exposure. Here, we report the results derived from 378 Yucheng subjects and 370 matched references.

RESULTS — The diabetes risk to members of the Yucheng cohort relative to their reference subjects was significantly increased for women (odds ratio [OR] 2.1 [95% CI 1.1–4.5]) but not for men after considering age, BMI, cigarette smoking, and alcohol intake. Yucheng women diagnosed with chloracne had adjusted ORs of 5.5 (95% CI 2.3–13.4) for diabetes and 3.5 (1.7–7.2) for hypertension compared with those who were chloracne free.

CONCLUSIONS — Yucheng women, who had endured previous exposure to PCBs and PCDFs, suffered from increased incidences of diabetes, particularly those who had retained significant levels of pollutant as evident from chloracne. When planning treatments against diabetes, the body burden of PCBs and dioxins should be carefully considered, especially for women.

Diabetes Care **31:1574–1579, 2008**

Type 2 diabetes is becoming more prevalent throughout the world, and although a number of conventional risk factors have already been identified, they can only partly explain such high levels of incidence. Polychlorinated biphenyls (PCBs) and dioxins are persistent organic pollutants (POPs) with long half-lives in the human body, and they may act as endocrine disruptors and exhibit endocrine system effects (1). The study of veterans of Operation Ranch Hand reported a higher dioxin level in diabetic patients compared with nondiabetic subjects (2). Longnecker et al. (3) revealed a 30% higher level of total PCBs in diabetic (primarily type 1) pregnant women than in nondiabetic subjects recruited in 1959–1966. Similar conclusions were drawn from the National Health and Nutrition Examination Survey (NHANES) (4) and other population studies in Belgium (5), Michigan (6), and Seveso, Italy (7). These data raised great concerns for public health (8) and promoted etiological research into the biological effects of POPs (9,10). Recently, the NHANES study in the U.S. showed striking dose-response relationships between the prevalence of diabetes and serum levels of six POPs, including PCB 153, dioxins, and organochlorine pesticides (OCPs) (11). Interestingly, severe obesity (BMI $\geq$30 kg/m^2) did not relate to an increased diabetes risk in those with undetectable levels of POPs. The cross-sectional study findings warrant a follow-up cohort study to assess the long-term effects of POPs on the risk of developing diabetes and hypertension. A mass poisoning occurred in central Taiwan after a quantity of rice-bran oil ingested in 1978–1979 was later found to be contaminated with PCBs and their heat-degraded byproducts (12). By the end of February 1983, there were 2,061 recorded cases of PCB poisoning, based on the symptoms and pathology of the illness, such as abnormally high levels of blood PCBs. The Yucheng ("oil disease") cohort was estimated to have consumed an average of 1 g (range 0.77–1.84) of PCBs and 3.8 mg polychlorinated dibenzofurans (PCDFs) during an average of nine months' exposure to the contaminated oil. Most (83%) of the blood levels ranged from 11 to 150 ppb. The current 24-year follow-up study of the Yucheng cohort provides a good opportunity to examine the hypothesis that raised levels of PCBs and dibenzofurans (DFs) might be associated with an increased risk of diabetes. Though obese people have been encouraged to reduce body weight by calorie restriction, serum levels of total PCBs have been shown to increase in the 6–9 months following the weight-loss program (13). Studying the effects of POPs on the degree of risk of type 2 diabetes is clearly relevant to managing both diabetes and obesity in modern societies.

RESEARCH DESIGN AND METHODS

— Beginning in 1992 and using the addresses listed for the 2,061 victims in the Yucheng registry obtained from the Taiwan Provincial Department

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Received 26 December 2007 and accepted 13 May 2008.
Published ahead of print at http://care.diabetesjournals.org on 16 May 2008. DOI: 10.2337/dc07-2449.

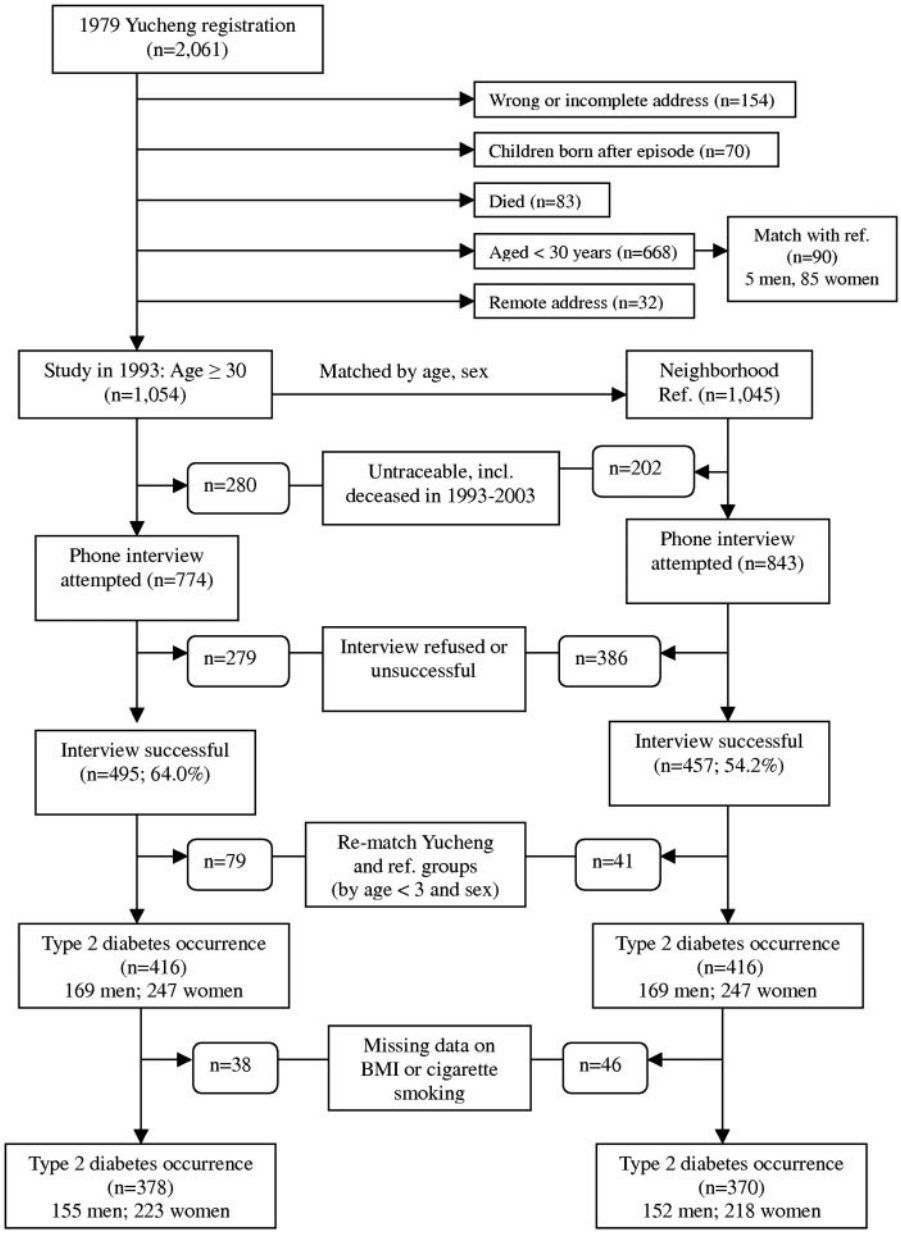

Figure 1—*Numbers of the Yucheng cohort and their matched reference group during 1979–2003.*

of Health, we attempted to locate each subject's record. Of these records, the addresses were wrong for 154 subjects, which prevented us from tracing those people, and a further 70 records had to be excluded because they belonged to the children of this Yucheng cohort (Fig. 1). A total of 83 subjects (8%) were deceased, 668 (66%) were aged less than 30, and 32 (3%) had a remote address. Individuals for the background-exposed groups were recruited in 1992 and matched against the Yucheng subjects for neighborhood (the same back in 1979), sex, age (no more than 3 years' difference), and exposure to POPs, such that none of the control individuals were in the original registration cohort (14). Between 1993 and 2003, we conducted a morbidity follow-up of the exposed subjects and their reference group with trained interviewers blinded to exposure status. Medical information on individuals who had been diagnosed or treated by certified medical doctors was acquired by telephone. The current study focused on individuals born before 1 January 1963 so as to examine the association between the cumulative incidence of type 2 diabetes and postnatal exposure to PCBs and PCDFs. We excluded 38 Yucheng subjects and 46 from their reference groups who were missing data on BMI or cigarette smoking, which are important risk factors for type 2 diabetes and hypertension, respectively. After all exclusions, 378 Yucheng and 370 matched reference subjects remained for analysis within the current study. We focused on those aged >30 years in the current study because type 2 diabetes is a chronic disease prevalent in the middle-aged population and because doing so prevents inclusion of subjects who could have had prenatal exposure to PCBs or PCDFs. Among the 668 subjects aged <30 years, there were 90 with a matched reference subject who could be successfully followed for a separate analysis. However, within this younger group, there were no diabetic subjects and just one hypertensive patient. We therefore omitted them from our current analysis.

Body burden of dioxins and PCBs

Total PCB levels were quantitated from serum samples originally collected by the Taiwan Provincial Department of Health in 1979–1983 (12). These serum samples ranged from 0.7 to 8.2 g (average 4.5 g) and were kept frozen at −20°C before analysis. Except for initial analyses carried out in Tokyo, all PCB levels were analyzed by the Food and Drug Bureau of the Department of Health Executive, Yuan, Taiwan. A Microtek 200 gas chromatography system was fitted with an electron capture detector (Ni ^{63}-ECD) and a glass column (3 mm × 2 mm) packed with Chromosorb WHP (80/100 mesh) coated with 3% OV-1. The temperatures of the inlet, column, and detector were maintained at 230, 200, and 280°C, respectively. The Webb-McCall method was adopted to quantify PCBs, with Kanechlor 500 used as a reference standard (15). For the background-exposed reference group, serum pooled from 50 subjects was analyzed using a high-resolution gas chromatography/high-resolution mass spectrometry method. Although we studied congener-specific profiles of PCBs and PCDFs in 1994 (16), we utilized information on total PCB levels measured at the time of the episode for the respective dosages that related to the cumulative incidence of disease.

Statistical methods

Student's *t*, Mann-Whitney *U* (if not normally distributed), and χ^2 tests were used to compare continuous and categorical variables between the exposed and reference groups. A univariate logistic regression model was used to calculate odds

Table 1—*General characteristics of the Yucheng cohort and their matched reference group aged ≥30 years in 1993*

	Men			Women		
	Yucheng	Reference group	*P*	Yucheng	Reference group	*P*
n	155	152	—	223	218	—
Age in 1993 (years)	59.6 ± 11.5	58.9 ± 11.5	ns	52.2 ± 10.6	51.6 ± 10.5	ns
<55	62 (40.0)	63 (41.5)	—	155 (69.5)	158 (72.5)	—
55–64	37 (23.9)	40 (26.3)	—	29 (13.0)	26 (11.9)	—
≥65	56 (36.1)	49 (32.2)	—	39 (17.5)	34 (15.6)	—
BMI (kg/m^2)	24.1 ± 3.1	24.0 ± 3.1	ns	24.3 ± 8.5	23.5 ± 3.4	ns
Education (years)	7.2 ± 4.1	7.2 ± 3.7	ns	6.6 ± 4.1	7.3 ± 4.2	ns
Current smoker	85 (55.2)	93 (62.0)	ns	2 (0.9)	1 (0.5)	ns
Alcohol drinking	41 (26.8)	34 (22.8)	ns	4 (1.8)	1 (0.5)	ns
Occupation						
None	70 (45.2)	59 (38.8)	ns	111 (49.8)	92 (42.2)	ns
Government	6 (3.9)	4 (2.6)	ns	7 (3.1)	8 (3.7)	ns
Agriculture	12 (7.7)	23 (15.1)	ns	5 (2.2)	6 (2.8)	ns
Manufacturing	54 (34.8)	53 (34.9)	ns	69 (30.9)	75 (34.4)	ns
Commercial	13 (8.4)	13 (8.6)	ns	31 (13.9)	37 (17.0)	ns
Serum PCBs (ppb)	73.3 ± 86.3	1.67*	—	87.4 ± 151.0	1.67*	—

Data are means ± SD or *n* (%). *General population had mean serum PCB levels of 1.67 ppb wet weight as previously reported using a pooled sample from 50 reference subjects (ref. 16). ns, not significant.

ratios (ORs) for diabetes prevalence among the exposed, relative to reference subjects, and multivariable logistic regression was used to evaluate the ORs with adjustments for potential confounding factors. For women, we did not carry out further adjustments for cigarette smoking (with only three smokers) and alcohol intake (with only five drinkers) in deriving a reliable model. We used JMP 5.0.1 software for all the analyses (SAS Institute, Cary, NC).

RESULTS — Table 1 shows very similar distributions in age, sex, BMI, education, lifestyle, and occupation between the Yucheng cohort and the background-exposed reference group. Mean PCBs in the Yucheng subjects were about 40- to 50-fold those of the reference group. Men appeared to be older than women by around 7 years. We suspected that men younger than 35 years old were too busy working to get registered for special care in 1979–1980.

The Yucheng subjects had a very high risk of developing chloracne compared with the reference group (Table 2). The AOR (OR adjusted for age and BMI in women and age, BMI, cigarette smoking, and alcohol drinking in men) of diabetes for the Yucheng cohort relative to the reference group remained significant in women (OR 2.1; $P < 0.05$) after adjusting for age and BMI. We found an age-adjusted OR of 6.4 ($P < 0.05$) in women aged >65 years who received diabetes therapy, which rose to 6.6 ($P < 0.05$) after further adjustment for BMI. For both sexes, there was a slight but nonsignificant increase in the risk of developing hypertension and cardiovascular disease. We compared the rate at which diabetes developed in subjects that exhibited chloracne with the rate in which it developed in those free of chloracne and found a highly significant age-adjusted OR of 4.6 (95% CI 1.9–11.4) and AOR of 5.5 (2.3–13.4) in women but not in men (Table 3). The same pattern was found for hypertension (AOR 3.5 [95% CI 1.7–7.2]) and cardiovascular disease (3.0 [1.5–8.6]).

CONCLUSIONS — We found that diabetes was twice as prevalent in Yucheng women who had been exposed to PCBs and PCDFs during the 1978–1979 poisoning as it was in the reference population in the long-term cohort study. The AOR significantly increased to 2.5 for those requiring therapy for diabetes and to 5.5 for those with chloracne, a condition symptomatic of POP poisoning. This correlation between POPs and diabetes is consistent with the findings from cross-sectional studies in Belgium (5) and the U.S. (2,4,11,17,25). In the current study, most excess body burdens of PCBs and PCDFs were present in women with an average age of 25 years, when type 2 diabetes most likely had not yet occurred. The cumulative incidence associated with PCB and DF exposure provides evidence that the exposure happened before onset of diabetes. However, caution should be exercised in interpreting the data because members of the Yucheng cohort group were accidentally exposed to PCBs and PCDFs for nearly a year via a diet of contaminated oil. These results might not apply to the background population, and further investigations are needed to control for the effects of different PCBs derived from sources other than those of the 1978–1979 poisoning. A recent report using the NHANES data showed significant association between non–dioxin-like PCBs and increased risk of insulin resistance in nondiabetic subjects, particularly those with a larger waist circumference (18). For those in the upper quartile of PCB 170 exposure, compared with the nondetectable reference group, the OR increased to 4.1 ($P < 0.01$). In the Yucheng cohort, a total of 33 PCB congener profiles showed that PCB 170 constituted 13% of all PCB concentrations (16). In addition to PCB 170, PCB 180 (which represented 14% of 33 PCBs), PCB 153 (13%), and PCB 156 (13%) each represented over 12% of the total PCBs. This implies that certain PCB congeners might be associated with an increased risk of diabetes occurrence.

We further report that Yucheng women diagnosed with chloracne have a significantly increased risk of developing hypertension and cardiovascular disease. This increased risk of hypertension may partly result from diabetes complications

involving cardiovascular disease. Prevalence of increased blood pressure was most strongly correlated with PCDFs, particularly 1,2,3,4,7,8-HxCDF in nondiabetic subjects in the NHANES study (22). This corresponded to data in the Yucheng cohort, in which 1,2,3,4,7,8-HxCDF (toxic equivalency factor 0.1) and 2,3,4,7,8-PeCDF (toxic equivalency factor 0.5) were important congeners, contributing ~20 and 50% of the total dioxins' toxic equivalent quotients (TEQs), respectively (16). This suggests that congeners containing PCDF or polychlorinated dibenzo-dioxins might be associated with an increased risk of hypertension.

The current study showed a nonsignificant association between PCB and DF exposure and type 2 diabetes occurrence in men, which is not consistent with findings of previous cross-sectional studies (11,17). In the Michigan follow-up study of the effects of exposing farmers and other households to animal feed contaminated with PCBs, women experienced twice the incidence of self-reported type 2 diabetes when total PCBs exceeded 5 ppb, but there was no increased diabetic risk for men (6). The 20-year follow-up study of the Seveso cohort, highly exposed to tetra-chlorinated dibenzo-*p*-dioxin after a factory incident in 1976 (7), showed that the mortality rate from diabetes had significantly doubled for women residing in the exposure area compared with women residing in the reference area but that the relationship was not present in men. It is notable that cigarette smoking was much more prevalent in the men involved in both our study and the Michigan study compared with the women who were investigated. Cigarette smoking has been found to activate the aryl-hydrocarbon receptor (19), which might be associated with the accelerated excretion of PCBs. Our study also showed slightly lower mean PCB and PCDF levels in men than in women. Further, women tend to have a greater fat percentage than men, which might result in a longer half-life of these lipophilic compounds. Obesity as a risk factor for diabetes might be attributable partly to the lipophilic compounds' storage in white adipose tissue (1). Fat tissue has been suggested to be a vehicle for increased diabetes risk (8). Women could also be more vulnerable to PCB and PCDF exposure as a result of higher estrogen levels than men. PCDFs, and some PCBs, can induce *CYP1A1* and *CYP1B1* gene expression by serving as aryl-hydrocarbon

Table 2—*Prevalence or ORs of reported diseases ever diagnosed by a physician in Yucheng, stratified by sex, in Taiwan from 1979–2003*

	Men				Women			
	Yucheng	Reference group	OR* (95% CI)	AOR	Yucheng	Reference group	OR* (95% CI)	AOR
n	155	152	—	—	223	218	—	—
Chloracne	66 (42.9)	1 (0.7)	117.0 (25.1–2,087)‡	111.5 (23.9–1,985)‡	51 (23.0)	0 (0.0)	—	—
Type 2 diabetes without therapy	22 (14.4)	22 (14.7)	1.0 (0.5–1.8)	1.0 (0.5–1.9)	25 (11.3)	12 (5.6)	2.2 (1.1–4.7)†	2.1 (1.1–4.5)†
Aged <55	3 (4.8)	7 (11.3)	0.4 (0.1–1.5)	0.5 (0.1–1.9)	7 (4.6)	7 (4.5)	1.0 (0.3–3.1)	1.0 (0.3–3.1)
Aged 55–64	9 (25.0)	5 (12.5)	2.3 (0.7–8.3)	3.7 (0.9–17.6)	6 (20.7)	0 (0.0)	—	—
Aged ≥65	10 (18.2)	10 (20.8)	0.8 (0.3–2.2)	0.8 (0.3–2.3)	12 (30.8)	5 (14.7)	2.6 (0.8–9.1)	2.6 (0.9–9.3)
Type 2 diabetes with therapy	22 (14.3)	17 (11.3)	1.3 (0.6–2.6)	1.3 (0.7–2.7)	17 (7.7)	7 (3.2)	2.5 (1.0–6.7)	2.5 (1.0–6.5)†
Aged <55	3 (4.8)	3 (4.8)	1.0 (0.2–5.7)	1.3 (0.2–7.5)	3 (2.0)	5 (3.2)	0.6 (0.1–2.5)	0.6 (0.1–2.5)
Aged 55–64	9 (25.0)	5 (12.5)	2.3 (0.7–8.3)	3.7 (0.9–17.7)	3 (10.3)	0 (0.0)	—	—
Aged ≥65	10 (17.9)	9 (18.8)	0.9 (0.3–2.5)	0.9 (0.3–2.6)	11 (28.2)	2 (5.9)	6.4 (1.5–43.9)†	6.6 (1.6–45.4)†
Hypertension with therapy	46 (30.0)	39 (26.0)	1.2 (0.7–2.0)	1.2 (0.7–2.0)	41 (18.5)	31 (14.4)	1.3 (0.8–2.3)	1.3 (0.8–2.2)
Hypertension without therapy	40 (26.0)	31 (20.7)	1.3 (0.7–2.4)	1.3 (0.8–2.4)	29 (13.1)	21 (9.7)	1.4 (0.7–2.7)	1.4 (0.8–2.5)
Cardiovascular disease	22 (14.2)	17 (11.2)	1.3 (0.6–2.6)	1.3 (0.7–2.6)	30 (11.6)	21 (9.6)	1.4 (0.8–2.6)	1.5 (0.8–2.7)

Data are *n* (%) unless otherwise indicated. *Age adjusted. †$P < 0.05$; ‡$P < 0.001$.

Table 3—*Lifetime prevalence of medical conditions in Yucheng individuals without (negative) or with (positive) reported chloracne aged ≥30 years, stratified by sex, in 2003*

	Men					Women				
	Negative	Positive	*P*	OR*	AOR	Negative	Positive	*P*	OR	AOR
n	95	72	—	—	—	186	58	—	—	—
Age (years)	61.6 ± 11.6	58.7 ± 11.5	0.2	—	—	52.3 ± 11.4	56.9 ± 9.7	0.006	—	—
BMI (kg/m^2)	24.2 ± 3.0	24.2 ± 3.2	1.0	—	—	24.2 ± 9.5	24.6 ± 3.3	0.7	—	—
Diabetes	11 (11.6)	12 (16.9)	0.2	1.7 (0.7–4.3)	1.7 (0.7–4.6)	11 (5.9)	14 (24.1)	0.0006	4.6 (1.9–11.4)‡	5.5 (2.3–13.4)‡
Hypertension	34 (35.8)	19 (26.4)	0.1	0.7 (0.4–1.5)	0.6 (0.3–1.1)	27 (14.4)	22 (37.9)	0.0009	3.3 (1.6–6.8)‡	3.5 (1.7–7.2)‡
Cardiovascular disease	14 (14.7)	12 (16.7)	0.8	1.3 (0.6–3.2)	0.9 (0.4–2.2)	22 (11.8)	15 (25.9)	0.0035	2.3 (1.1–4.8)‡	3.0 (1.5–8.6)‡
PCBs (ppb)	53.9 ± 53.2	94.4 ± 106.9	0.004	—	—	72.6 ± 114.7	121.4 ± 202.8	0.04	—	—

Data are *n* (%), means ± SD, or OR (95% CI). *Age adjusted. ‡$P < 0.001$.

receptor agonists (19). *CYP1A1* and *CYP1B1* catalyze hydroxylation of the A-ring of estradiol (E_2) to form the catechol estrogen 2- or 4-hydroxyl estradiol (2-OH-E_2 or 4-OH-E_2, respectively), which may be altered by exposure to dioxins (20). The metabolism of 4-OH-E_2 via redox-active compounds generates free radicals, such as reactive semiquinone intermediates. Free radicals are known to cause increased oxidative stress, which has been associated with a range of vascular pathologies, including hypertension and diabetes (21). Further investigations aimed at identifying and dissecting the various POP detoxification pathways are clearly warranted.

Dioxin-like chemicals relating to diabetes may involve an estrogen-dependent peroxisome proliferator–activated receptor (PPAR) pathway (23). Tetrachlorinated dibenzo-*p*-dioxin cotreating estrogens were found to upregulate insulin-like growth factor binding protein-1 (IGFBP-1) in MCF-7 cells via the PPAR pathway (24). These compounds may counter the effects of insulin, which downregulates IGFBP-1. Dioxins or dioxin-like chemicals may therefore disrupt glucose homeostasis.

A hypertriglycemia state, often coexisting with hypertriglycerides, might be related to delayed degradation and/or excretion of the lipophilic compounds in diabetic patients. In addition, metabolism of PCB- and DF-related genes, such as *CYP1A*, *CYP1B*, and *CYP11B* (19,20), may relate to the development of chloracne and later chronic conditions of hyperglycemia and hypertension. Further study of these genetic polymorphisms related to the effect of susceptibility is suggested.

There might be confounding factors, such as OCPs (18), which are often correlated with PCBs/DFs because of a similar exposure route in humans. Nonetheless, levels of 1,1-dichloro-2,2-bis (*p*-chlorophenyl)ethylene (DDE) were slightly lower in Yucheng women (means ± SD 6,380 ± 620 ppb) compared with their neighborhood reference subject (8,700 in pooled serum samples [Prof. Yueliang Leon Guo, personal communication]). Potential confounding effects from OCPs are therefore unlikely.

The effects of aging could have influenced this 24-year follow-up study, since members of the exposure group would be expected to die sooner from diabetes and/or cardiovascular disease. This influence might be slight, as we found that only one man and six women died from diabetes among all registered Yucheng subjects (25). Additionally, the women appeared to be younger than the men by ~7 years. One possibility for future study would be to select a group of younger women; this might reduce the statistical power in women because diabetes and hypertension are generally less prevalent in the younger age-group. Nonetheless, we have established the increased risk for women compared with men; thus, our study is unlikely to have a biased conclusion.

The present study did not include other disease-related lifestyle features, such as exercise and total calorie intake, which might relate to differences in personal socioeconomic status and an altered risk of diabetes. We used neighborhood reference subjects as a background exposure group. Furthermore, BMI, education, and occupational distribution were similar between the exposed and reference groups. A previous study showed that lipid contents were similar between the two groups (16). We would expect the same conclusion after adjustments for differences in lipids, exercise, and total calorie intake.

In conclusion, an increased cumulative incidence of type 2 diabetes was seen among Yucheng women who had been exposed to PCBs and PCDFs, particularly among those diagnosed with chloracne. In modern societies, the body burden of PCBs and dioxins clearly needs to be considered within the framework of diabetes prevention. The effects of female sex and genetic factors warrant further investigation.

Acknowledgments— This study was supported by a National Taiwan University Hospital research grant and National Science Council Grant #96-2314-B-002-100-MY2, and the National Health Research Institutes, Taiwan, EO-096-PP-13.

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