

Null Results in Brief

The Ratio of Specific Polychlorinated Biphenyls as a Surrogate Biomarker of Cytochrome P4501A2 Activity—A Pharmaco-Metabonomic Study in Humans

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Introduction

The activity of cytochrome P4501A2 (CYP1A2) may be an important determinant of risk for certain cancers (1, 2). Phenotyping procedures, such as the caffeine breath test (CBT), have advantages over genotyping and have been used to characterize CYP1A2 activity in epidemiologic studies (1). The large-scale use of these methods, however, is limited by several factors, including high cost, a complicated analytic procedure, and interference by dietary caffeine (1, 3). CYP1A2 metabolizes certain polychlorinated biphenyls (PCB; ubiquitous environmental contaminants), such as PCB118 and PCB105, but not others, such as PCB153 (4). Ayotte et al. (5) recently reported that the serum concentration ratio of PCB105/PCB153 and that for PCB118/PCB153 significantly decreased with CYP1A2 activity, measured using a CBT among 20 subjects. They hypothesized that these ratios maybe useful surrogate biomarkers of CYP1A2 activity (6); in this article, we tested their hypothesis using data from a much larger study (7).

Materials and Methods

Subjects. The study population consisted of Mohawk men and women from the Mohawk Nation at Akwesasne, a Native American community along the St. Lawrence River in New York, Ontario, and Quebec (7). Briefly, of the 111 Mohawk women who became

pregnant between April 1, 1992 and March 31, 1995 and of the 139 Mohawk men who were husbands or close relatives of the women, 172 agreed to undergo a CBT. After exclusion of participants who had a history of heart disease, stroke, seizure disorders, uncontrolled hypertension, arrhythmia, hepatitis, jaundice or other types of liver disease, adverse reaction to caffeine, chemotherapy within the past 5 y, currently taking prescription medications (not including oral contraceptives), or who were currently breast-feeding, the CBT was administered to 103 persons. Information about demographic characteristics, height and weight, diet, and use of medications, alcohol, caffeine, and cigarettes was collected. Each participant signed an informed consent form.

Measurement of PCBs. A 20-mL nonfasting blood specimen was used for serum PCB analysis. Sixty-eight PCB congeners were determined with gas chromatography with electron capture detection (7). The limits of detection were 0.02 ng/g wet weight for PCB153 and 0.01 ng/g for PCB118 and PCB105.

Caffeine Breath Test. CYP1A2 activity was measured with a CBT (7). Labeled caffeine ($[3-^{13}\text{C}]$ methyl) was given in a dose of 3 mg/kg, up to a maximum of 200 mg. A 20-mL breath sample of expired air was collected immediately before and 30 and 60 min after ingestion of the labeled caffeine. After cryogenic purification of the CO_2 present in the exhaled air samples, the $^{13}\text{CO}_2$: $^{12}\text{CO}_2$ ratio was determined by differential gas isotope ratio mass spectrometry (8). The excess ^{13}C was calculated from the ratio found in the breath sample before and after ingestion of the substrate and expressed as the dose exhaled per hour.

Statistical Analysis. When the level of a given PCB congener was below the limit of detection, half of the limit of detection value for that congener was imputed. PCB153 serum concentrations (pg/g wet weight) were divided by PCB118 or PCB105 to get ratios (PCB153/PCB118 and PCB153/PCB105) predicted to be directly proportional to CYP1A2 activity. Spearman correlations between CBT level and ratios were calculated. Multiple linear regression models of \log_{10} -transformed CBT were

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Table 1. Characteristics of subjects in the present study and the Ayotte et al. study (5)

	Present study	Ayotte study
Sample size (<i>n</i>)	103	40*
Median PCB concentration (pg/g lipid)		
153	46 [†] (258 pg/g wet weight) [‡]	766
118	8 [†] (55 pg/g wet weight) [‡]	145
105	1 [†] (<LOD) [‡]	32
PCB congener ratios		
153/118	4.7 (0.3-127.8)	NR
153/105	43.0 (2.0-430.8)	NR
Median and range of CBT level (% of dose)	1.6 (0.1-6.1) per hour	5.3 (1.9-9.6) per 2 h
Race	Native Americans	Caucasians
Gender (male, %)	61	60
Mean age (y)	28	47
Mean BMI (kg/m ²)	26	27
Current smoking (%)	42	43
Current alcohol consumption (%)	55	NR
Current caffeine consumption (%)	66	NR

NOTE: Numbers in parentheses are ranges.

Abbreviations: LOD, limit of detection; NR, not reported; BMI, body mass index.

*Only 20 subjects with CBT data were included in Spearman correlation analysis.

[†] *n* = 46 (with lipid-adjusted concentration).

[‡] Unadjusted concentrations in 103 subjects.

fitted, with adjustment for the potential confounders age, gender, body mass index, smoking, and usual consumption of alcohol and caffeine.

Results

Whereas PCB153 was detectable in the serum of 100 (97%) participants, detection frequencies were lower for PCB118 (33%) and PCB105 (10%). Unadjusted and lipid-adjusted median concentrations of the three PCB congeners (Table 1) were similar to levels in the U.S. general population (9). Given the lower proportion detected for PCB105, the ratio of PCB153/PCB105 was much higher than that for PCB153/PCB118.

CBT level was correlated with PCB153/PCB105 ($r = 0.22$; $P = 0.02$; $n = 103$) but not PCB153/PCB118 ($r = 0.12$; $P = 0.22$; $n = 103$). A stronger correlation was found between CBT and PCB153 ($r = 0.34$; $P = 0.001$) than with PCB118 ($r = 0.14$; $P = 0.27$) or PCB105 ($r = 0.13$; $P = 0.20$). In the regression models (Table 2), associations were not found between CBT level and PCB congener ratios. Current smoking and male sex, however, were associated with higher CBT values ($P < 0.05$).

Discussion

Whereas Ayotte et al. (5) found Spearman correlations between CBT and PCB153/PCB118 ($r = 0.53$; $P = 0.02$) and PCB153/PCB105 ($r = 0.62$; $P = 0.003$), we found smaller associations in this larger study ($r = 0.12$ and 0.22 , respectively). Ayotte et al. (5) found that PCB118 and PCB105 concentrations were inversely correlated with CBT levels, whereas Fitzgerald et al. (7) did not. We also note that Fitzgerald et al. (7) found a direct association between PCB153 and CBT, whereas Ayotte et al. (5) did not.

The inconsistent findings between the present study and the Ayotte et al. (5) study may be explained by differences in sample size, PCB exposure level, and race. The size of the Ayotte et al. (5) study may not have given enough statistical power to detect an association between CBT and PCB153, which may have relatively low potential to induce CYP1A2 and is little or not metabolized by CYP1A2. The subjects in the Ayotte et al. (5) study were more highly exposed (at least 15-fold higher than those in the present study) to PCBs through fish consumption. That the associations between CBT and PCB118 and PCB105 were found by

Table 2. Coefficients from linear regression models of log₁₀-transformed CBT in 103 subjects

Models	β	SE (β)	<i>P</i>
Model I			
PCB153/PCB118	-0.0005	0.001	0.68
Model II			
PCB153/PCB105	-0.0004	0.0004	0.39
Covariates			
Age (y)	0.001	0.003	0.65
BMI (kg/m ²)	-0.009	0.007	0.24
Males (vs females)	0.16	0.076	0.035
Current smoking (packs/d)	0.28	0.077	0.002
Alcohol consumption (no. alcohol drinks/d)	-0.0004	0.004	0.92
Amount of regular coffee in past year (cups/wk)	0.003	0.003	0.25

NOTE: Two separate models were run using PCB153/PCB118 (model I) and PCB153/PCB105 (model II) as independent variables. Covariate coefficients from model I (shown) were similar to those in the model II.

Ayotte et al. (5) but not by Fitzgerald et al. (7) suggests that PCB118 and PCB105 can induce the CYP1A2 enzyme involved in their own metabolism only when present at higher levels or that the levels of these PCBs were so low in the present study that measuring the full extent of variability was not possible. In addition, the subjects in the Ayotte et al. (5) study were Caucasians and they may have higher CYP1A2 activity than do Asians and Native Americans (10). Furthermore, CYP1A2 activity may be more easily induced in Caucasians than in other populations, such as African-Americans, Chinese, and, we speculate, Native Americans (1).

In summary, PCB ratios were not correlated with CYP1A2 activity in this population. For subjects with greater PCB body burdens or different genotypes, however, the utility of PCB ratios as surrogate biomarker of CYP1A2 activity remains to be determined.

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