Polychlorinated Biphenyls, Cytochrome P4501A1 Polymorphism, and Postmenopausal Breast Cancer Risk[1]

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Abstract

In experimental systems, polychlorinated biphenyls (PCBs) induce cytochrome P4501A1 (*CYP1A1*), which is involved in metabolism of steroid hormones and polycyclic aromatic hydrocarbons in humans. A genetic polymorphism coding for a valine to isoleucine substitution in exon 7 has been associated with lung cancer risk in Japanese populations. In a previous study, we found no association between *CYP1A1* genotype and breast cancer risk. However, we were interested in determining whether genotype would relate to risk when PCB body burden was taken into account. In a subset of a case-control study in western New York, 154 postmenopausal women with incident, primary, histologically confirmed postmenopausal breast cancer and 192 community controls were interviewed and underwent phlebotomy. Serum levels of 56 PCB peaks were determined by high resolution gas chromatography with electron capture. PCR-RFLP analyses of the *CYP1A1* polymorphism were performed. Unconditional logistic regression was used to compute adjusted odds ratios and 95% confidence intervals. Among women with serum PCB levels above the median of the distribution in the control group, there was increased risk of breast cancer associated with the presence of at least one valine allele, compared with women who were homozygous for the isoleucine alleles (odds ratio, 2.93; 95% confidence interval, 1.17–7.36). Among women with low PCB body burden, no association between *CYP1A1* genotype and breast cancer risk was observed. Adjustment for serum lipids and body mass index did not affect the magnitude of the observed associations. PCB body burden may modify the effect of the polymorphism on postmenopausal breast cancer risk through increased *CYP1A1* enzyme induction or by activation by specific PCB congeners. These results should be considered preliminary, pending replication by other studies.

Introduction

It has been proposed that higher body burden of PCBs[3] may increase the risk of breast cancer because of their hypothesized estrogenic (1), tumor-promoting (2), immune-modulating (3), and enzyme-inducing properties (4). To date, however, findings from epidemiological investigations of this relationship have been inconclusive, with several studies showing no association with risk, and others showing risk only among specific subgroups of individuals (5–13).

In laboratory studies, PCBs are potent inducers of *CYP1A1*, a drug-metabolizing gene, involved in the activation of potentially genotoxic endogenous and exogenous substances (14, 15). There is wide interindividual variation in *CYP1A1* activity, and several genetic polymorphisms are present. Approximately 10–15% of Caucasians carry a *CYP1A1* valine for isoleucine substitution allele (16). Although no difference in enzymatic activity of the variant type compared with the wild type has been demonstrated (17), there is evidence that the *CYP1A1* variant genotype results in *CYP1A1* activity that is more inducible in lymphocytes (18). Greater activity may lead to enhanced carcinogen activation and steroid hormone metabolism and may, therefore, be potentially related to risk for breast cancer. The *CYP1A1* valine for isoleucine substitution has been associated with greater risk of lung cancer in Japanese (19). For breast cancer, there is no evidence for an overall association between this genetic polymorphism and breast cancer risk (20–24), although two studies reported subgroup effects among light smokers (22) or among women who had commenced smoking before age 18 (24).

In this case-control study, we sought to examine whether body burden of PCBs modified the association between *CYP1A1* genotype and breast cancer risk.

Materials and Methods

Study Population. This research used a subset of data collected as part of a case-control study (1986–1991) of 933 postmenopausal Caucasian women in Western New York; detailed methods have been reported previously (25). The protocol for the study was reviewed by the Institutional Review Board of the State University of New York at Buffalo and of participating hospitals. Informed consent was received from all participants. Women diagnosed with incident, primary, histologically confirmed breast cancer (n =

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[3] The abbreviations used are: PCB, polychlorinated biphenyl; CYP1A1, cytochrome P450 1A1; OR, odds ratio; CI, confidence interval.

Table 1 Risk of postmenopausal breast cancer associated with PCB body burden, Western New York 1986–1991

	Case	Control	Crude OR	95% CI	Adj. OR[a]	95% CI
			PCBs			
Low[b]	70 (46)	96 (50)	1.0		1.0	
High[c]	84 (54)	95 (50)	1.12	0.79–1.86	1.27	0.76–2.14
Total	154 (45)	191 (55)				
			Cyp1A1 genotype			
Ile:Ile	127 (83)	168 (88)	1.0		1.0	
Ile:Val or *Val:Val*	27 (17)	23 (12)	1.56	0.86–2.85	1.79	0.91–3.55
Total	154 (45)	191 (55)				

[a] ORs adjusted for age, education, serum lipids, age at menopause, family history of breast cancer, age at first birth, parity, duration of lactation, body mass index, and smoking status.
[b] 0.75–3.72 ng/g of serum.
[c] 3.73–19.04 ng/g of serum.

439) were frequency-matched by age and county of residence with controls ($n = 494$), randomly selected from the New York State Motor Vehicle lists (<65 years) and the Health Care Finance Administration rolls (≥65 years). Interview data included medical, reproductive, and lifestyle histories. Of women who provided usable interviews, ~63% agreed to donate a blood sample. Blood was drawn for 262 postmenopausal breast cancer cases and 319 controls. Controls providing a blood sample did not differ from those who did not with respect to age, years of education, age at menarche, prevalence of benign breast disease or family history of breast cancer, and fruit, vegetable, or meat consumption, although they tended to have fewer years of smoking, consume fewer alcoholic beverages, and undergo menopause at an older age.

A subset of stored blood specimens was used for toxicological and genetic analyses: 154 women with postmenopausal breast cancer and 191 controls. Cases were only included in the final study sample if their blood was drawn before chemotherapy or radiation and within 3 months of surgery. Controls were frequency matched to cases by date of blood draw (±3 months) and age (±3 years). Controls who provided a blood sample but were not selected for these analyses were more likely to consume red meat and alcoholic beverages than those who were selected, but the two groups differed little with regard to demographic, reproductive, or lifestyle characteristics.

PCB Analysis. PCB concentrations were determined by the method of Greizerstein *et al.* (26). Total PCBs were calculated from summing the detected levels of 56 congener peaks, measured in the serum (based on 73 individual congeners). Participants with nondetectable levels for individual PCBs were assigned zero for these compounds. The procedures include standardized extraction, clean up, and quantification by high-resolution gas chromatography and comprehensive quality assurance program to minimize systematic and random errors. The sample was mixed with solutions containing IUPAC isomers 46 and 142 (surrogate standards). Methanol was added to precipitate the proteins, and the resulting mixture was extracted with hexane. The extract was concentrated and then cleaned by passing through a Florisil column. The eluate was then evaporated to a small volume, and isomers 30 and 204 were added as internal standards. An aliquot of the mixture was injected into the gas chromatographic system equipped with an electron capture detector. Quantification was based on calibration standards and response factors calculated using purchased reference materials. Quality control activities consisted of analyses of samples in batches of 6–10 simultaneously with quality control samples. The coefficients of variation of the quality control samples for individual PCB congeners ranged from 2.5% (IUPAC 180) to 6.2% (IUPAC 52). The coefficient of variation for total PCBs was 1.8%. The quality assurance program checked that the procedures were under control by the use of control charts and set criteria for data acceptability. The limit of detection for each analyte was determined as the mean of background noise plus three SDs in five reagent blank samples.

Genetic Analysis. As described previously (22), DNA was extracted from blood clots obtained after centrifugation and removal of serum, which had been stored at −70°C. The *CYP1A1* isoleucine-to-valine substitution in exon 7 was determined simultaneously with that of glutathione *S*-transferase (GSTM1), as detailed previously (22). Briefly, using primers specific for GSTM1 and for *CYP1A1*, where a base was substituted to introduce an *Nco*I restriction site, genes were amplified using PCR. The amplified PCR product was subjected to restriction enzyme analysis with *Nco*I (New England Biolabs, Beverly, MA), according to the manufacturer's instructions. A simultaneous restriction enzyme digestion was also conducted with *Hin*fI (New England Biolabs), which cleaved the GSTM1 fragment so that this band did not overlap the cleaved *CYP1A1* fragment. Analysis by gel electrophoresis [4.0% agarose; 3:1 NuSieve (FMC Bioproducts, Rockland ME); agarose (Life Technologies, Inc., Gaithersburg, MD)] revealed 232- and 31-bp fragments for wild-type alleles (isoleucine) or a single 263-bp fragment when the mutation (valine) was present. The assay was validated by confirming polymorphic Mendelian inheritance patterns in seven human family cell lines ($n = 134$ family members), encompassing three generations (data not shown; samples were obtained from the National Institute General Medical Scientist Human Genetic Mutant Cell Repository, Coriell Institute, Camden, NJ). Genotyping results were read by two independent investigators, and genotyping for 20% of the subjects was repeated for quality control. The investigators were blinded to each other's interpretations and to case-control status.

Statistical Analyses. Descriptive analyses included Student *t* tests of means for cases and controls for lifestyle, reproductive, and dietary variables and χ^2 tests for categorical variables. We carefully examined cases and controls with respect to age and date of blood draw and attempted to individually match study participants on these variables. However, the width of the frequency matching strata did not allow for individual matching. Therefore, we used unconditional logistic regression to calculate ORs and 95% CIs. ORs were adjusted for potential confounders, including age, education, family history of breast cancer, parity, quetelet index, duration of lactation, age at first birth, serum lipids, and smoking status (nonsmokers; light

Table 2 Risk of postmenopausal breast cancer by *CYP1A1* polymorphism and PCB body burden, Western New York 1986–1991

PCB/*CYP1A1*	Case	Control	Crude OR	95% CI	Adj. OR[a]	95% CI
PCB low[b]-Ile:Ile	62 (41)	85 (45)	1.0		1.0	
PCB low[b]-Ile:Val/Val:Val	8 (5)	11 (6)	1.0	0.37–2.62	0.88	0.29–2.70
PCB high[c]-Ile:Ile	65 (42)	83 (43)	1.07	0.68–1.70	1.08	0.62–1.89
PCB high[c]-Ile:Val/Val:Val	19 (12)	12 (6)	2.17	0.98–4.78	2.9	1.18–7.45
Total	154 (45)	191 (55)				

[a] ORs adjusted for age, education, serum lipids, age at menopause, family history of breast cancer, age at first birth, parity, duration of lactation, body mass index, and smoking status homozygous (Ile:Ile) for the *CYP1A1* wild-type alleles.
[b] 0.75–3.72 ng/g of serum.
[c] 3.73–19.04 ng/g of serum.

smokers, <29 pack-years; and heavy smokers, 29 or more pack-years). Covariates were only included in the final regression model if they were established risk factors in these data or changed the observed risk estimate by at least 15%. Lipid adjustment was modeled after the method described by Phillips *et al.* (27), where serum triglycerides and total cholesterol levels were used to estimate total serum lipid content. *CYP1A1* was investigated by collapsing the categories for women who were homozygous (*Val:Val*) with those who were heterozygous (*Ile:Val*) for the valine allele because of the small number of women in the first group ($n = 6$). Participants were designated as having either high or low PCB body burden on the basis of a level above or below the median for the controls. Levels ranged from 0.75 to 3.72 ng/g of serum in the low PCB group and from 3.73 to 19.04 ng/g of serum in the high PCB group.

Results

The effects of PCBs on risk (13) and of *CYP1A1* (22) have been examined in detailed elsewhere. Shown here are those associations in this subsample with both *CYP1A1* and PCB determinations. Women with higher body burden of PCBs were not at greater risk of breast cancer than women with lower levels, and women with at least one valine *CYP1A1* allele (*Ile:Val* or *Val:Val*) were at slightly elevated risk compared with women who were homozygous for the isoleucine allele (*Ile:Ile*; Table 1). The test for statistical interaction between PCB body burden and *CYP1A1* genotype approached statistical significance ($P = 0.13$). In Table 2, the combined effect of of PCB body burden and *CYP1A1* genotype is shown. Women with lower serum PCB levels and *CYP1A1 Ile:Ile* served as the reference category. Compared with this group, women with lower PCB levels and *CYP1A1* valine genotype were not at greater risk for breast cancer (adjusted OR, 0.88; 95% CI, 0.29–2.70), nor were women with elevated PCB levels and *CYP1A1 Ile:Ile* (OR, 1.08; 95% CI, 0.62–1.89). In contrast, there was evidence of increased risk for women with high PCB body burden and at least one valine allele when compared with women with lower serum PCB levels and who were homozygous for the isoleucine allele (OR, 2.96; 95% CI, 1.18–7.45). We repeated these analyses in two PCB congener groups, defined by *CYP1A1* induction activity (IUPAC nos. 60, 105, 118, 128, 138, 153, 180, and 203) and by potential estrogenic activity (IUPAC nos. 18, 47, 52, 77, 136, and 153). The ORs for women with elevated PCB body burden and at least one valine allele were 2.87 (95% CI, 1.19–7.30) and 2.75 (95% CI, 1.09–7.21), respectively (data not shown). This correspondence in the observed risk estimates is likely to be an effect of the high correlations between total PCB levels and measured levels of these specific congener (Pearson $r > 0.90$).

Discussion

In this study of associations between serum levels of PCBs, *CYP1A1* genotype, and breast cancer risk, we found that among women with elevated PCB body burden, the *CYP1A1* polymorphism statistically significantly increased risk. No effect of *CYP1A1* was noted among women with lower serum levels of PCBs or women with the *Ile:Ile* genotype. To our knowledge, this is the first study to examine the effect of *CYP1A1* in relation to PCB exposure on breast cancer risk. A number of previous investigations found no main effect between *CYP1A1* and breast cancer among Caucasian women (20–24), despite laboratory evidence for a role of PAHs, which are activated by *CYP1A1*, in mammary carcinogenesis. *CYP1A1* is also known to be involved in the metabolism of estradiol to the possibly mutagenic catechol estrogens (28), and increased metabolism related to the polymorphism could increase breast cancer risk through that mechanism. It is possible that such an association was masked by variability in *CYP1A1* induction, due to heterogeneity in exposures to PCBs and other *CYP1A1* inducers.

As indicated above, results of investigations of PCBs and breast cancer have been mixed; a number of studies did not observe an increase in breast cancer risk associated with elevated PCB levels (6, 7, 11, 12). Interestingly, in one of those studies (12), there was suggestion of an association between exposure and risk among African-American women. Investigators have identified novel *CYP1A1* alleles in African-Americans, and the *Msp*I allele, which is thought to be in linkage disequilibrium with the exon 7 substitution, is three times as common among African-Americans as among Caucasians (16) and has been found to be associated with increased breast cancer risk (21). It is possible that risk associated with PCB exposure among African-American women may be related to the increased prevalence of mutant alleles within this population.

The role of PCBs as P450 inducers in experimental animals has been so widely acknowledged that the commercial form is often used in animal studies to ensure and hasten neoplasms initiated by known carcinogens. Repeated studies, using a number of different bioassays and target organs, have all confirmed the role of PCBs as promoters of carcinogenesis (4). Caucasian postmenopausal women with elevated PCB body burden and the *CYP1A1* isoleucine-to-valine substitution are possibly at greater risk of breast cancer because of the PCB-mediated enhanced induction of polymorphic *CYP1A1*, leading to increased activation of environmental carcinogens and subsequently resulting in the production of reactive intermediates and DNA damage. Thus, by inducing *CYP1A1*, PCBs and other inducers can trigger the activation of xenobiotics, such as those found in tobacco, into mutagenic compounds. This notion is supported by our observation that risk was significantly increased among women with elevated PCB body burden and the *CYP1A1* polymorphism who had ever

smoked cigarettes (OR, 7.74; 95% CI, 1.12–53.90) but not among women who had never smoked (OR, 1.43; 95% CI, 0.53–3.87; data not shown). It should be pointed out, however, that these risk estimates are based on very small numbers, as indicated by the width of the corresponding confidence intervals, and should be interpreted with caution.

Alternatively, there is some evidence that P450-mediated metabolism of lower chlorinated PCBs, which have been associated with greater toxicological activity, may lead to further metabolism by peroxidases to DNA-reactive metabolites (29). It is possible that women with both elevated PCB body burden and the potentially more inducible *CYP1A1* variant genotype are at greater risk for DNA damage and subsequently for breast cancer. In fact, in our previous analyses, we observed a modest increase in risk (OR, 1.66) for women with detectable levels of lower chlorinated PCBs (13). We attempted to examine the effect of lower chlorinated PCBs in this research, but only a small proportion of participants had detectable levels for these congeners, resulting in very small numbers, which did not permit further stratification by *CYP1A1* genotype.

Sample size was a major limitation in this study, as in many molecular epidemiological studies. Our findings were based on small numbers, resulting in possibly unstable risk estimates. It is possible that the modifying effect of PCB body burden may be a result of sampling variation. Furthermore, it was not possible to examine the effect of PCB body burden on the association between *CYP1A1* and risk in more detail, restricting the analysis to crude stratification into low and high PCB body groups. A larger sample size would allow for an examination of a potential threshold effect at which PCB body burden affects the association between *CYP1A1* and risk. Finally, due to sample size restrictions, it was not feasible to explore the interactions identified previously of PCBs with lactation status (13) and *CYP1A1* genotype and smoking status (22) in this study of both PCBs and *CYP1A1* genotype.

Overall, our results indicate that the *CYP1A1* isoleucine-to-valine substitution may be a risk factor for breast cancer among women with elevated PCB body burden. If these findings are confirmed, the lack of an association between PCBs and breast cancer in some studies may, in part, be explained by the fact that only a small proportion of the study population was susceptible to the adverse effects of PCB exposure, *i.e.*, those with the *CYP1A1* polymorphism.

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