Risk of Brain Tumors in Children and Susceptibility to Organophosphorus Insecticides: The Potential Role of Paraoxonase (PON1)

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Prior research suggests that childhood brain tumors (CBTs) may be associated with exposure to pesticides. Organophosphorus insecticides (OPs) target the developing nervous system, and until recently, the most common residential insecticides were chlorpyrifos and diazinon, two OPs metabolized in the body through the cytochrome P450/paraoxonase 1 (PON1) pathway. To investigate whether two common PON1 polymorphisms, C-108T and Q192R, are associated with CBT occurrence, we conducted a population-based study of 66 cases and 236 controls using DNA from neonatal screening archive specimens in Washington State, linked to interview data. The risk of CBT was nonsignificantly increased in relation to the inefficient PON1 promoter allele [per PON1-108T allele, relative to PON1-108CC odds ratio (OR) = 1.4; 95% confidence interval (CI), 1.0–2.2; p-value for trend = 0.07]. Notably, this association was strongest and statistically significant among children whose mothers reported chemical treatment of the home for pests during pregnancy or childhood (per PON1-108T allele: among exposed, OR = 2.6; 95% CI, 1.2–5.5; among unexposed, OR = 0.9; 95% CI, 0.5–1.6) and for primitive neuroectodermal tumors (per PON1-108T allele: OR = 2.4; 95% CI, 1.1–5.4). The Q192R polymorphism, which alters the structure of PON1 and influences enzyme activity in a substrate-dependent manner, was not associated with CBT risk, nor was the PON1-108T/Q192R haplotype. These results are consistent with an inverse association between PON1 levels and CBT occurrence, perhaps because of PON1’s ability to detoxify OPs common in children’s environments. Larger studies that measure plasma PON1 levels and incorporate more accurate estimates of pesticide exposure will be required to confirm these observations. Key words: brain tumor, children, chlorpyrifos, diazinon, dried blood spots, Guthrie cards, paraoxonase, pesticides, PON1, xenobiotic metabolism. Environ Health Perspect 113:909–913 (2005). doi:10.1289/ehp.7680 available via http://dx.doi.org/[Online 18 March 2005]

Some epidemiologic studies have observed increased risk of childhood brain tumors (CBTs) in relation to home pesticide use, farm residence, or parental occupation in agriculture (Bunin et al. 1994; Corder et al. 2001; Davis et al. 1993; Efrid et al. 2003; Holly et al. 1998; Kristensen et al. 1996; Pogoda and Preston-Martin 1997). Organophosphorus insecticides (OPs) target the nervous system, and it is possible that CBT occurrence is associated with prenatal or childhood exposure to OPs or a reduced ability to metabolize them. One important OP-detoxifying enzyme is paraoxonase 1 (PON1). Present in the liver and blood, PON1 hydrolyzes the acetylcholinesterase-inhibiting oxons (activated intermediates) of some OPs, including chlorpyrifos and diazinon (Costa et al. 2002), which are important in agriculture and in recent decades were the most common insecticides used in homes and yards (Donaldson et al. 2002). Although some environmental exposures influence PON1 activity (Costa et al. 2005), they appear to have much less effect than genetic variation (Jarvik et al. 2002); thus, PON1 levels are relatively stable after they reach adult levels at 6–15 months of age (Cole et al. 2003).

The PON1 gene contains several common single nucleotide polymorphisms, some of which directly affect OP metabolism. In the promoter region, adjacent to a binding site for the transcription factor Sp1 (Deakin et al. 2003), the C-108T polymorphism influences expression of the gene, with the PON1-108T allele conferring reduced PON1 levels. It is the most influential known polymorphism in the promoter region, contributing 22–25% of variation in PON1 expression in white adults (Brophy et al. 2001; Levie and James 2000). Relative to PON1-108CC homozygotes, PON1-108T homozygotes have, on average, 33–45% lower enzyme activity as adults (Brophy et al. 2001; Levie and James 2000) and 63% lower as neonates (Chen et al. 2003). PON1’s OP detoxification activity is also influenced by enzyme structure, and a coding region polymorphism, Q192R, determines whether glutamine (Q) or arginine (R) is present near PON1’s catalytic center (Harel et al. 2004). The two resulting PON1-192 isoforms hydrolyze some substrates at different rates. In mice, PON1 R192 isoform provides significantly better protection than does PON1 Q192 from chlorpyrifos oxon (Li et al. 2000). The two isoforms provide similar protection with respect to the oxon of diazinon. Because chlorpyrifos and diazinon are common in children’s environments (Andrew Clayton et al. 2003) and PON1 genotype may influence susceptibility to these OPs (Cole et al. 2003), we examined whether the inefficient PON1 promoter allele (PON1-108T) or the allele coding for the PON1-192 isoform may provide lower chlorpyrifos protection (PON1-192R) associated with increased risk of CBT in children.

Materials and Methods

Subject identification and specimen collection. Institutional review board approvals were received from the Fred Hutchinson Cancer Research Center and Washington State Department of Health (WDOH) before the conduct of this study. Most subjects were drawn from a previous case–control study (Gurney et al. 1996), with additional control subjects randomly selected from similar birth years. Briefly, in the previous study, cases were diagnosed with primary tumors of the brain, cranial nerves, or meninges [International Classification of Diseases for Oncology (ICD-O; World Health Organization [WHO] 1976), codes 191.0–192.1] at < 20 years of age in 1984–1991 while residing in the Seattle–Puget Sound region of Washington State covered by a population-based cancer incidence registry affiliated with the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. Controls from the same counties were identified via random digit dialing (RDD), frequency matched to cases 2:1 by sex and age. Mothers of all participating children (134 (74%) eligible cases and 268 controls) were interviewed to determine recent home pesticide use. This information was confirmed by linking interview data to the WDOH from neonatal screening archive specimens in Washington State, linked to interview data. The risk of CBT in children.

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281 (79%) eligible controls] were interviewed using a structured questionnaire that included questions about home pesticide treatment, defined as chemical treatment of the house for pests such as termites, fleas, ants, cockroaches, or silverfish, during the index pregnancy and/or childhood up to the diagnosis date (cases) or similar reference date (controls).

A subset of these subjects [70 (52%) cases and 160 (57%) controls] were eligible for the present study because the child was born after 1977 and the mother resided in Washington when the child was born, so a dried blood spot (DBS) card potentially remained archived at the WDOH Newborn Screening Program. Blind to case status, staff located cards and clipped a DBS for 66 (94%) eligible cases and 137 (86%) eligible controls. Most (74%) of the unlocated subjects were born either in the earliest, uncatalogued months (14 of 27) or outside a civilian hospital (6 of 27). Case-control, race/ethnicity, and histologic tumor type proportions from the previous study were preserved in the subset for whom DBS were available. Subjects’ DBS were permanently anonymized (American Society of Human Genetics 1996) before removal from WDOH. DBS from a pilot study that randomly sampled 100 anonymous infants from the same archives and a similar range of birth years (1980–1991) were available to supplement our control group.

**DNA extraction and genotyping.** DNA extraction and genotyping were conducted at the Center for Ecogenetics and Environmental Health Functional Genomics Laboratory at the University of Washington, blind to case status. Six 3-mm punches were removed from each DBS, with all instrumentation flame sterilized between specimens. DNA was then extracted using the QIAamp DNA Mini Kit (QIAGEN, Valencia, CA) according to the manufacturer’s DBS protocol.

**PON1 C-108T and Q192R variants** were identified with TaqMan detection system-based assays (respective probes from Integrated DNA Technologies, Coralville, IA, and Applied Biosystems, Foster City, CA). Genotypes were assigned based on relative fluorescence, verified by sequencing as needed. Negative controls and DNA-sequenced positive controls representing each possible genotype were included in each batch of analyses. We included blind duplicate or quadruplicate specimens for 6% of cases and 6% of interviewed controls. All PON1 genotypes were represented, and the results were in complete agreement with the original specimens. In addition, the laboratory repeated the assays for >10% randomly selected specimens, also in full agreement.

PON1 genotyping was completed for all subjects. One control for whom we collected two equally well-matching DBS was excluded from our CBT–PON1 analyses because PON1 genotype was different for the two possible matches. Thus, 66 cases and 236 controls were available for statistical analysis.

**Statistical analysis.** Genotype and allele frequencies were tabulated, and chi-square tests were used to check Hardy-Weinberg equilibrium. Using Intercooled Stata (version 8.0; Stata Corp., College Station, TX), we conducted logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for CBT in relation to PON1 genotype (Breslow and Day 1980). Because PON1 heterozygotes have an intermediate phenotype (Brophy et al. 2001; Leivest and James 2000), each polymorphism was modeled linearly (0, 1, or 2 PON1_108T alleles; 0, 1, or 2 PON1_192Q alleles). To allow for possible threshold effects (e.g., any vs. no PON1_192Q isoform), the appropriateness of the linear assumption was verified using the likelihood-ratio test and by comparing modeled risk estimates to those obtained for individual genotypes. Test of trend p-values for CBT and number of PON1_108T or PON1_192Q alleles were derived from the linear terms in the logistic regression models.

To consider the possible combined effect of the two polymorphisms, we investigated whether risk estimates for one polymorphism depended on the other and calculated CBT risk estimates in relation to PON1_108T/Q192R diplotype and haplotypes. For the latter, we modeled the number of each allele (TQ, TR, CQ, CR) linearly, using all subjects for whom haplotype could be directly inferred or accurately estimated (PHASE, version 2.0.2) (Stephens et al. 2001). We also used PHASE to test whether cases and controls had different haplotype frequencies.

CBT (Gurney et al. 1999) and the PON1_108T and PON1_192Q alleles (Brophy et al. 2002; Chen et al. 2003) are more common in non-Hispanic whites than in whites of most other races or ethnicities. To investigate whether population stratification influenced risk estimates, we repeated all analyses restricted to children whose biologic mother and father were both non-Hispanic white. Race/ethnicity was not otherwise included in models because there were few nonwhite or Hispanic subjects, and within this heterogeneous category for which prevalence of PON1 variants varies widely, there were substantial racial/ethnic differences between cases and controls.

Other potential confounders considered were the other PON1 polymorphism (C-108T by Q192R, and vice versa) and the frequency-matching variables (sex and age). These were retained in the models only if ORs or 95% CIs for the PON1 polymorphisms were altered by >10%, and unless stated, unadjusted risk estimates are presented. We also examined whether CBT–PON1 risk estimates varied by reported home pesticide treatment, farm or residential, or parental agricultural occupation, potential indicators of exposure to OPs metabolized by PON1. Statistical interaction on the multiplicative scale was assessed in logistic regression models by the p-value (α = 0.05) of the interaction term, or likelihood-ratio test when a single interaction required multiple terms. To the extent possible, we calculated risk estimates by histologic subtype: astroglial tumors (ICD-O histology codes 9380–9384, 9400–9421, 9424–9442), primitive neuroectodermal tumors (PNETs; 9362, 9470–9473, 9500), and other CBTs, using all controls as the reference group (WHO 1976).

**Results**

**Subject characteristics.** Approximately half of cases had astroglial tumors, with the remainder evenly divided between PNETs and a heterogeneous group of other tumors (Table 1). Most cases (71%) were diagnosed before the age of 5 years. Similar proportions of cases (88%) and controls (91%) were non-Hispanic white; however, among subjects for whom the father’s race/ethnicity was known (63 cases, 135 interviewed controls), proportionally fewer cases (81%) than controls (93%) were born to two non-Hispanic white parents.

Proportionally fewer mothers of cases (31%) than controls (42%) reported that any of the child’s homes had ever been chemically treated for pests during the pregnancy or childhood before the diagnosis/reference date. In this largely urban/suburban region, few subjects had ever lived on a farm (9% cases, 3% controls) or had parents who worked in agriculture (14 cases, 10% controls).

**PON1 genotype.** PON1 genotype frequencies did not significantly differ from Hardy-Weinberg equilibrium (both p > 0.20). Proportionally more cases (26%) than controls (17%) were homozygous for the inefficient PON1 promoter allele (PON1_108TT), and risk of CBT was nonsignificantly increased with increasing PON1_108TT alleles (for PON1_108TTT, relative to PON1_108CC: OR = 2.1; 95% CI, 0.9–4.7; for PON1_108CT, OR = 1.4; 95% CI, 1.0–2.2; p-value for trend = 0.07; Table 2). The association was strongest and statistically significant in relation to the PNET histologic tumor type specifically (for each additional PON1_108TT allele: OR = 2.4; 95% CI, 1.1–5.4; p-value for trend = 0.03, based on 15 PNET cases, including 6 PON1_108TTT homozygotes and 7 heterozygotes; data not shown). According to PON1_192Q genotype, 48% cases and 42% controls had no PON1_192Q isoform (Table 2). Although there was a weak suggestion of increased CBT risk in relation to increasing number of PON1_192Q alleles, CIs were quite wide and the p-value for trend was nonsignificant (for PON1_192QQ relative to PON1_192RR: OR = 1.5; 95% CI, 0.6–3.4; for PON1_192QR: OR = 1.2; 95% CI, 0.8–1.9;
Risk of CBT in relation to PON1 C-108T and Q192R polymorphisms [n (%)].

| Race/ethnicity | Cases (n = 66) | Interviewed controls (n = 136) | Anonymous controls (n = 100) | All controls (n = 236) |
|---------------|---------------|-------------------------------|-------------------------------|------------------------|
| White         | 58 (88)       | 131 (96)                      | 33 (75)                       | 164 (91)               |
| Black         | 0 (0)         | 2 (1)                         | 4 (9)                         | 6 (3)                  |
| Hispanic      | 0 (0)         | 1 (1)                         | 5 (11)                        | 6 (3)                  |
| Asian         | 3 (5)         | 0 (0)                         | 2 (5)                         | 2 (1)                  |
| Other         | 5 (8)         | 2 (1)                         | 0 (0)                         | 2 (1)                  |
| Male          | 42 (64)       | 84 (62)                       | 57 (58)                       | 141 (60)               |
| Birth year    |               |                               |                               |                        |
| 1970–1983     | 30 (45)       | 71 (52)                       | 50 (50)                       | 121 (51)               |
| 1984–1991     | 36 (55)       | 65 (48)                       | 50 (50)                       | 115 (49)               |
| Age at diagnosis/reference (years) |         |                               |                               |                        |
| < 5           | 47 (71)       | 88 (65)                       | —                             | —                     |
| 5–10          | 19 (29)       | 47 (35)                       | —                             | —                     |
| Mother smoked during pregnancy |         |                               |                               |                        |
|               | 10 (15)       | 23 (17)                       | —                             | —                     |
| Pesticide exposure indicators |         |                               |                               |                        |
| Home pesticide treatmentb | 20 (31)%       | 57 (42)                       | —                             | —                     |
| Farm residencec | 6 (9)         | 4 (3)                         | —                             | —                     |
| Parental agricultural occupationd | 9 (14)       | 14 (10)                       | —                             | —                     |
| Histologic tumor type |         |                               |                               |                        |
| Astroglial    | 37 (56)       | —                             | —                             | —                     |
| PNET          | 15 (23)       | —                             | —                             | —                     |
| Other         | 14 (21)       | —                             | —                             | —                     |

Discussion

This small population-based study suggests that having an inefficient PON1 promoter allele at position –108 is associated with an increased risk of CBT. The observed association was strongest with respect to PNET, the CBT type most consistently associated with farm residence (Bunin et al. 1994; Kristensen et al. 1996). For the most part, CBT was not associated with the PON1Q192R polymorphism, which determines the enzyme’s structure and thereby detoxification efficiency for some substrates. Our results were similar when we focused on the largest racial/ethnic group in our population, indicating that potential biases related to race/ethnicity were probably not largely responsible for our observations. In addition, risk estimates were fairly resilient to exclusion of either of the two population-based sources of controls. Nevertheless, any

Table 2. Risk of CBT in relation to PON1 C-108T and Q192R polymorphisms [n (%)].

| PON1 genotype | Cases (n = 66) | Controls (n = 236) | OR (95% CI) | Subjects with white parentsa |
|---------------|---------------|-------------------|-------------|----------------------------|
| C-108T: PON1 promotion |         |                   |             |                          |
| TT (efficient) | 17 (26)       | 29 (17)           | 2.1 (0.9–4.7) | 14 (27)                   |
| CT (intermediate) | 34 (52)   | 125 (52)          | 1.4 (1.0–2.2) | 28 (55)                   |
| CC (efficient) | 15 (23)       | 72 (31)           | 1.0 (reference) | 9 (18)                    |
| Q192R: PON1R192 isoform |         |                   |             |                          |
| QQ (none)    | 32 (48)       | 100 (42)          | 1.5 (0.6–3.4) | 27 (53)                   |
| QR (some)    | 28 (42)       | 105 (44)         | 1.2 (0.8–1.9) | 21 (41)                   |
| RR (all)     | 8 (12)        | 31 (13)           | 1.0 (reference) | 3 (6)                     |

aBiologic mother and father both reportedly non-Hispanic and white; excludes 3 cases, 1 interviewed control, and 180 anonymous controls for whom father’s race/ethnicity unknown. bFor individual genotypes, with each polymorphism modeled linearly (0, 1, or 2 PON1C-108T alleles; 0, 1, or 2 PON1R192 alleles) using logistic regression. cAdjusted for PON1C-108T.
association between CBT and \textit{PON1}_{C-108T}, and the lack thereof between CBT and \textit{PON1}_{Q192R}, must be interpreted with caution.

First, our small numbers of subjects may have hampered our ability to observe a CBT–\textit{PON1}_{Q192R} association and simultaneously increased the probability that the apparent association between CBT and \textit{PON1}_{C-108T} is a false positive. Furthermore, no prior studies have examined this relationship. Non-Hodgkin lymphoma (Kerridge et al. 2002), multiple myeloma (Linz et al. 2004), and prostate cancer (Antognelli et al. 2004; Marchesani et al. 2003) have been associated with other \textit{PON1} polymorphisms, including Q192R, but to our knowledge this is the first cancer study to consider the C-108T polymorphism of \textit{PON1}, and the first study to examine the potential role of this enzyme in relation to childhood cancer.

Second, we obtained subjects’ DNA from an indirect source. It is possible that environmental DNA contamination occurred, which would likely bias risk estimates toward null. However, our assays do not simply detect the presence of an allele, but instead rely on relative amounts of each allele compared with sequence-verified laboratory controls to assign one of three genotypes.

Third, although our specimen retrieval rate for cases was very high and did not require survival-related selection bias among cases in the study from which they were drawn. However, even if such bias existed and \textit{PON1} genotype influenced cancer prognosis, it is unlikely this could account fully for the moderately strong association we observed between CBT and \textit{PON1}_{C-108T}.

To the extent that this association is not due to chance or case survival, these results suggest that CBT risk may be inversely related to \textit{PON1} enzyme levels. Ideally, fresh blood would have been available and \textit{PON1} enzyme levels measured, but the C-108T polymorphism is a significant determinant of \textit{PON1} levels in both neonates and pregnant women (Chen et al. 2003). Because \textit{PON1} may hydrolyze OPs before they can reach the brain, our results lend support to prior epidemiologic studies that have observed an increased risk of CBT in relation to possible pesticide exposure. OPs target the developing nervous system (Garcia et al. 2002; Johnson et al. 1998), and chlorpyrifos may affect replication and differentiation of glial cells (Garcia et al. 2001).

If OPs do relate to CBT, we would expect CBT–\textit{PON1} associations to be present mainly among those exposed to chlorpyrifos and/or diazinon. These two OPs were the most common residential insecticides during the study years, and indoor air is an important source of children’s exposure to them (Andrew Clayton et al. 2003). Therefore, it is interesting that we observed an increased risk of CBT in relation to the inefficient \textit{PON1}_{C-108T} allele only among children whose homes were reportedly treated for insect pests. Still, one cannot discount the possibility that this OP-metabolizing enzyme could protect the brain via its more generic ability to metabolize oxidized lipid molecules. That \textit{PON1}_{Q192R} was not associated with CBT seems to underscore this point. However, the relative protection provided by the two resulting \textit{PON1} isoforms depends on the OP (Li et al. 2000), and perhaps other factors such as \textit{PON1} levels. We had no direct measures of these, nor of the level of exposure to chlorpyrifos and diazinon. Because of our modest number of cases, we also had limited ability to consider other potentially relevant factors, such as diet, age at diagnosis, family history of cancer, and prenatal and childhood exposure to tobacco smoke. For example, there was some indication that the \textit{PON1}_{Q192R} allele is associated with increased risk of CBT among subjects reportedly not exposed to tobacco smoke, but we could not adequately examine whether this reflects a plausible biologic effect or is simply a spurious observation due to chance or bias related to racial/ethnic differences between cases and controls and smokers and nonsmokers.

The strengths of our study are population-based identification of cases and controls, the use of a DNA source unrelated to case survival, and inclusion of children diagnosed before the residential phase-out of chlorpyrifos and diazinon began. Future studies of CBT and \textit{PON1} would benefit from larger sample sizes, more accurate indicators of exposure to chlorpyrifos and diazinon, the addition of other \textit{PON1} polymorphisms, measurement of plasma \textit{PON1} activity (e.g., \textit{PON1} status) (Costa and Furlong 2002), and genotyping/phenotyping of both children and mothers. It would also be useful to know whether the \textit{PON1}_{C-108T} polymorphism is associated with biomarkers of relevance to cancer, such as chromosome aberrations, as has been demonstrated in farmers with respect to \textit{PON1}_{Q192R} (Au et al. 1999). Such studies would be worthwhile in light of the possible association we observed between CBT occurrence and the predominant polymorphism in the \textit{PON1} promoter region, and because chlorpyrifos remains a leading agricultural insecticide and is detected in or on foods frequently consumed by children (Andrew Clayton et al. 2003; U.S. Department of Agriculture 2004).

### Table 3. Risk of CBT in relation to \textit{PON1}_{C-108T} genotype, by ever/never chemical treatment of home for insect pests during pregnancy or childhood.

| Home pesticide treatment | \textit{PON1}_{C-108T} genotype | Cases | Controls | OR (95% CI) | OR (95% CI) |
|--------------------------|--------------------------------|-------|----------|-------------|-------------|
| Yes                      | TT                             | 9 (43) | 10 (18) | 1.4 (0.5–3.9) | 6.5 (1.5–29.7) |
|                          | CT                             | 8 (40) | 26 (46) | 0.5 (0.2–1.3) | 2.6 (1.2–5.5) |
|                          | CC                             | 3 (15) | 21 (37) | 0.2 (0.1–0.7) | 1.0 (reference) |
| No                       | TT                             | 7 (16) | 13 (16) | 0.8 (0.3–2.7) |             |
|                          | CT                             | 26 (58) | 47 (59) | 0.9 (0.5–1.6) |             |
|                          | CC                             | 12 (27) | 19 (24) | 1.0 (reference) |             |

*Based on maternal interview; chemical treatment of home for termites, fleas, cockroaches, ants, silverfish, or other, during index pregnancy or during childhood before diagnosis/reference date. Excludes one case for whom home pesticide treatment was unknown. Within respective pesticide category. Excludes anonymous controls, due to absence of pesticide interview data. Relative to \textit{PON1}_{192RR} homozygotes whose homes were not chemically treated for insect pests. Relative to \textit{PON1}_{192QR} homozygotes whose homes were chemically treated for insect pests.

### Table 4. Risk of CBT in relation to \textit{PON1}_{Q192R} genotype, by ever/never chemical treatment of home for insect pests during pregnancy or childhood.

| Home pesticide treatment | \textit{PON1}_{Q192R} genotype | Cases | Controls | OR (95% CI) | OR (95% CI) |
|--------------------------|--------------------------------|-------|----------|-------------|-------------|
| Yes                      | QQ                             | 8 (40) | 26 (46) | 0.8 (0.2–2.4) | 0.6 (0.1–3.3) |
|                          | QR                             | 10 (50) | 27 (47) | 1.0 (0.3–2.7) | 0.8 (0.4–1.8) |
|                          | RR                             | 2 (10) | 4 (7)    | 1.2 (0.3–5.2) | 1.0 (reference) |
| No                       | QR                             | 23 (51) | 33 (42) | 1.7 (0.6–5.4) |             |
|                          | RR                             | 18 (40) | 37 (47) | 1.3 (0.7–2.3) |             |
|                          | RR                             | 4 (9)   | 9 (11)   | 1.0 (reference) |             |

*Based on maternal interview; chemical treatment of home for termites, fleas, cockroaches, ants, silverfish, or other, during index pregnancy or during childhood before diagnosis/reference date. Excludes one case for whom home pesticide treatment was unknown. Within respective pesticide category. Excludes anonymous controls, due to absence of pesticide interview data. Relative to \textit{PON1}_{192RR} homozygotes whose homes were not chemically treated for insect pests. Relative to \textit{PON1}_{192QR} homozygotes whose homes were chemically treated for insect pests.

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