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Polycyclic aromatic hydrocarbons and postmenopausal breast cancer: an evaluation of effect measure modification by body mass index and weight change

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Abstract

Background—Polycyclic aromatic hydrocarbons (PAHs) have been linked to breast cancer in many, but not all, previous studies. PAHs are lipophilic and stored in fat tissue, which we hypothesized may result in constant low-dose exposure to these carcinogens. No previous studies have evaluated whether obesity modifies associations between multiple measures of PAHs and breast cancer incidence.

Methods—This population-based study included 1,006 postmenopausal women with first primary *in situ* or invasive breast cancer and 990 age-frequency matched controls. To evaluate effect modification by obesity (adult body mass index (BMI, kg/m^2) and weight change) on multiple PAH measures (the biomarker PAH-DNA adducts, and long-term sources active cigarette smoking, living with a smoking spouse, grilled/smoked meat intake, residential synthetic log

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Documentation of Institutional Review Board (IRB) Approval

IRB approval #15-1675 was gained for the ancillary study reported here on 08/10/2015 at the University of North Carolina. Written signed informed consent was obtained from participants prior to conducting the interview for the parent study, Long Island Breast Cancer Study Project.

burning, and vehicular traffic), interaction contrast ratios (ICRs) for the additive scale, and ratio of odds ratios (RORs) with log-likelihood ratio tests (LRT) for the multiplicative scale, were determined using unconditional logistic regression.

Results—BMI modified the PAH-DNA adduct and postmenopausal breast cancer association on the additive (ICR: 0.49; 95% CI: 0.01, 0.96) and multiplicative (ROR: 1.56; 95% CI: 0.91, 2.68) scales. The odds ratio for detectable vs. non-detectable adducts was increased among women with BMI ≥25 (OR=1.34; 95% CI: 0.94, 1.92), but not in those with BMI <25 (OR=0.86; 95% CI: 0.57, 1.28) (LRT p=0.1). For most other PAH measures, the pattern of modification by BMI/weight gain was similar, but estimates were imprecise.

Conclusions—The association between PAH-DNA adducts and breast cancer incidence may be elevated among overweight/obese women.

Keywords

Polycyclic aromatic hydrocarbons; Breast cancer; Obesity; Weight gain; Adducts

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants that result from the incomplete combustion of organic material. Ambient PAH are combustion products of burning organic material. Common exposure sources include motor vehicle exhaust, grilled/smoked food, both active and passive cigarette smoke, and indoor stove and fireplace use (Mumtaz and George, 1995). Tobacco smoke, both active and passive, is a major contributor to ambient PAH exposure (IARC, 2010; White et al., 2016). However, diet may be the most common contributor to PAH exposure in non-smokers (Bostrom et al., 2002; White et al., 2016). The Environmental Protection Agency has determined a list of 16 priority PAHs of which seven PAHs have been classified as probable carcinogens, and the International Agency for Research on Cancer has classified PAHs as known carcinogens to the lung (IARC, 2010).

Associations between ambient PAH measures and breast cancer incidence among women are now relatively consistent. Historically, epidemiologic studies between active smoking and breast cancer were inconsistent (Luo et al., 2011b; Reynolds et al., 2004), but a recent meta-analysis of cohort studies reported a modest increase in breast cancer incidence for former and current active smoking (Gaudet et al., 2013) and the US Surgeon General Report states that evidence is suggestive for a causal relationship between active smoking and breast cancer (US Department of Health and Human Services, 2014). Long-term environmental tobacco smoke (ETS) has been more consistently associated with breast cancer incidence (Johnson, 2005; Reynolds et al., 2009; Terry and Rohan, 2002) and the Long Island Breast Cancer Study Project (LIBCSP) reported a doubling of risk for living with a smoking spouse for ≥27 years (Gammon et al., 2004a). PAH-DNA adducts are a biomarker of recent exposure and reflect DNA damage, a step in carcinogenesis. Detectable PAH-DNA adducts, or their proxy, have been consistently linked to breast cancer in previous studies (Gammon et al., 2004b; Li et al., 1999; Rundle et al., 2000b), with one exception (Saieva et al., 2011). Cooking food through grilling and smoking leads to the formation of PAHs (Knize et al.,

1999) and has been associated with breast cancer incidence (Steck et al., 2007). Similarly, residential burning of synthetic logs contributes to indoor air pollution and was found to increase breast cancer risk in a case-control study (White et al., 2014). Outdoor air pollution from the combustion of vehicular fuels also contributes to ambient PAH exposure. In the LIBCSP, a validated emissions model assessed exposure to residential traffic-related benzo[a]pyrene levels (a PAH used as a proxy for all traffic related PAHs). Women in the top 5% of exposure compared to women below the median had an increased odds of breast cancer (Mordukhovich et al., 2015), consistent with other studies on air pollution exposures and breast cancer (Bonner et al., 2005; Crouse et al., 2010; Hystad et al., 2015; Nie et al., 2007).

PAHs are lipophilic and can be stored in the fat tissue of the breast (Goth-Goldstein, 2010; IARC, 2010). We hypothesized that individuals with higher amounts of body fat may store and metabolize PAHs to a different extent than those with lesser amounts of body fat. The mechanism may be that fat tissue serves as a reservoir where PAHs can accumulate (Mumtaz and George, 1995). It is plausible that PAHs stored in fat tissue are a source of constant low-dose exposure to these carcinogens. One study to date has addressed this issue focusing only on active smoking and obesity (Luo et al., 2011a). Therefore, the aim of the study reported here was to determine if the associations between multiple measures of PAH exposure and breast cancer are modified by multiple measures of body size among postmenopausal women.

2. Methods

This study used case-control resources from the LIBCSP, a population-based study which was designed to examine relationships between environmental exposures and breast cancer in Nassau and Suffolk counties, New York. Detailed methods of the parent case-control study have been described previously (Gammon et al., 2002a). Institutional Review Board approval was obtained from all participating institutions.

2.1. Study Population

To be eligible for the LIBCSP, all women had to be English speakers and residents of either Nassau or Suffolk counties in New York at the reference date (the time of diagnosis for cases or identification for controls). Cases were newly diagnosed with first primary *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. Cases were identified through daily or weekly contact with the pathology departments of 31 hospitals in the Long Island-New York City area that diagnose/treat women with breast cancer. Controls were women without a personal history of breast cancer, and were frequency matched to the expected distribution of case women by 5-year age group. Potentially eligible controls were identified by random digit dialing for those under age 65 and from the Health Care Financing Administration for those 65 years of age or older. All participants signed an informed consent form prior to interview.

LIBCSP participants included 1,508 cases and 1,556 controls (82.1% and 62.7% of all eligible subjects, respectively) whose ages ranged from 20 to 98 years. In the study population, the distribution of self-identified race was 93% white, 5% black, and 2% other,

which is similar to the distribution in the source population from which it arose at the time of data collection (Gammon et al., 2002a). The study reported here was conducted using the 1,006 cases and 990 controls who were postmenopausal at the reference date. We restricted our ancillary study to postmenopausal women because BMI, a modifier in this analysis, is positively associated with postmenopausal (Carmichael and Bates, 2004), but not premenopausal breast cancer (Cheraghi et al., 2012). As previously reported in the LIBCSP, postmenopausal breast cancer has been associated with parity (Shantakumar et al., 2007b), breastfeeding (Shantakumar et al., 2007b), hormone replacement therapy (HRT) use (Shantakumar et al., 2007a), physical activity (McCullough et al., 2012), postmenopausal BMI (McCullough et al., 2015), and weight gain (Eng et al., 2005).

2.2. PAH Exposure Assessment

The main case-control questionnaire lasted approximately 120 minutes, and was administered by trained interviewers to all respondents in their homes. For cases, this occurred on average within 3 months of their first primary breast cancer diagnosis. Additionally, peripheral blood samples were donated at the time of the interview by 73.1% of cases and 73.3% of controls.

Six measures of PAHs were considered in our study: the biomarker PAH-DNA adducts, and long-term sources including active cigarette smoking, residential ETS, grilled/smoked meat intake, residential synthetic log use, and vehicular traffic exposure. Information on active and passive smoking, grilled/smoked meat, synthetic log use, and residential history (used to determine vehicular traffic exposure) were assessed as part of the main case-control questionnaire, whereas the PAH-DNA adducts were assessed using DNA isolated from the blood samples.

2.2.1. Active/Passive Smoking—Individuals were asked whether they had ever smoked at least 1 cigarette per day for 6 months or longer and were classified as ever smokers (current and former) or never smokers. Passive smoke exposure was assessed as whether individuals ever lived with a smoker, including a smoking spouse. Passive smoke from a spouse was the source of residential ETS of longest exposure duration among LIBCSP participants, and had the strongest association with breast cancer (Gammon et al., 2004a).

2.2.2. Grilled/Smoked Food Intake—As part of the main questionnaire, women were asked to report their consumption of four groups of PAH-containing foods: smoked beef, lamb, and pork; grilled/barbequed beef, lamb, and pork; smoked poultry or fish; and grilled/barbequed poultry or fish. Consumption was averaged over 6 decades of life to determine each individual's average annual intake. This exposure variable was dichotomized into 0–54 and 55+ servings per year based on findings from a previous LIBCSP report (Steck et al., 2007).

2.2.3. Synthetic Log Use—Individuals were queried about whether they had used an indoor stove or fireplace ≥3 times per year at each of their Long Island residences across the life course, and what material was burned. The study reported here focuses on whether

individuals had ever used synthetic logs in their stove/fireplace because this material had the strongest association with breast cancer in a previous LIBCSP study (White et al., 2014).

2.2.4. Vehicular Traffic—The geographic model developed, and validated, to estimate vehicular traffic exposure specifically for the LIBCSP respondents, has been described in detail previously (Beyea et al., 2006; Beyea et al., 2005; Mordukhovich et al., 2015). Briefly, all addresses at which a woman resided in Nassau and Suffolk counties for at least one year were geocoded. The model was constructed to determine exposure for a study participant's Long Island residences in and before 1995. The model incorporated information on road networks and transportation patterns, United States (U.S.) vehicular PAH emissions data, pollutant dispersion factors, and Long Island, NY meteorological details to determine predicted residential ambient B[a]P concentrations, a surrogate for all traffic related PAHs. Individuals were classified as $<95^{th}$ percentile or $\geq 95^{th}$ percentile of exposure in 1995 because this categorization was the best representation for the association with breast cancer (Mordukhovich et al., 2015; White et al., 2016).

2.2.5. PAH-DNA Adducts—The PAH-DNA adduct assay requires at least 25 ml of blood, and thus, biomarker assays were completed for 1,157 (n= 572 cases, 585 controls) postmenopausal participants. Established risk factors for breast cancer did not differ between women who donated blood and women whose DNA was available for this assay (Gammon et al., 2002b). Assays were conducted in two rounds using competitive ELISA with the laboratory personnel blinded to case-control status, using methods described previously (Gammon et al., 2004b; Gammon et al., 2002b). For the study reported here, individuals were classified as having detectable or non-detectable PAH-DNA adducts because this cut-point yielded the strongest association with breast cancer incidence (Gammon et al., 2004b).

2.3. Effect Measure Modifier Assessment

Two potential effect measure modifiers of the PAH source-breast cancer association were considered, using data collected as part of the main questionnaire: BMI at one year before the reference date, and weight change from age 20 to one year before the reference date.

2.3.1. Weight change—Individuals were classified as maintained weight (within +/− 3kg) or gained weight (>3kg). Only 36 cases and 61 controls lost weight and because the current study evaluates weight change as a modifier of PAHs, the stratification of these 36 cases across categories of PAH exposure results in small cell sizes. Further, because the risk of breast cancer associated with weight loss is not consistent with the risk for those who maintained weight (Eng et al., 2005), it is possible that we could introduce bias if the two groups were collapsed together into the same exposure category. Therefore, individuals who lost weight were eliminated from the analysis.

2.3.2. BMI—Women were dichotomized as <25 kg/m^2 and ≥ 25 kg/m^2 (which corresponds to the World Health Organization (WHO) definitions for "underweight"/ "normal" weight vs. "overweight"/ "obese", respectively). This cut-point is based on a functional form analysis we conducted comparing Lowess plots (Jacoby, 2000), likelihood ratio tests (Vittinghoff et al., 2005), and Akaike Information Criterion (AIC) (Bozdogan, 1987) for the

binary categorization, continuous, WHO standard BMI categories (<18.5, 18.5–24.9, 25.0–29.9, and ≥30.0) (World Health Organization, 1995), and restricted cubic spline (Durrleman and Simon, 1989) coding modeled against case status. It was determined that the binary form maintained comparable model fit.

2.4. Confounder Assessment

Potential confounders were determined from a review of the literature and development of a directed acyclic graph (DAG) (Greenland et al., 1999; Shrier and Platt, 2008). The minimally sufficient adjustment set (Greenland et al., 1999) included alcohol intake (ever/never), marital status (ever/never), parity (continuous), education (categorical: less than high school, high school, some college, college graduate, post college), and total energy intake (continuous). Total energy was assessed as part of a self-administered 101-item modified Block FFQ, which was completed by 98% of cases and 98% of controls at the time of the case-control interview (Gammon et al., 2002a). Other potential confounders were assessed as part of the interviewer-administered main case-control questionnaire.

2.5. Statistical Analysis

Unconditional logistic regression (Hosmer and Lemeshow, 1989) was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between each of the six PAH measures and postmenopausal breast cancer. All models were adjusted for the frequency matching factor, 5-year age group. Multivariable models also included the minimally sufficient confounder adjustment set described above.

Effect measure modification (EMM) by BMI and weight change, for each PAH-breast cancer association considered, was evaluated on both the additive and multiplicative scales. For EMM on the additive scale, single-referent models were constructed to compute interaction contrast ratios (ICRs) and corresponding 95% CIs (Hosmer and Lemeshow, 1992; Rothman et al., 2008). To analyze EMM on the multiplicative scale, models with and without the body size*PAH interaction term were compared to compute the likelihood ratio test (LRT) with α=0.05 (Hosmer and Lemeshow, 1989). Stratified models were also constructed to compute ratios of odds ratios (RORs) and 95% CIs (Heilbron, 1981), as an additional measure to indicate heterogeneity on a multiplicative scale (Fleiss, 1994).

All analyses were completed in SAS 9.4 (Cary, NC).

3. Results

Multivariable and age-adjusted effect estimates were similar. The multivariable results are shown in Tables 1–3, and the results adjusted for age only are shown in the Supplementary Tables S1–S2.

As shown in Table 1, the multivariable odds ratios for the associations between the six PAH measures and postmenopausal breast cancer, adjusted for a common set of potential confounders, are similar to the LIBCSP effect estimates previously reported (which had been adjusted for measure-specific confounders only) (Gammon et al., 2004a; Gammon et al., 2004b; Mordukhovich et al., 2015; Steck et al., 2007; White et al., 2014). Specifically, the

odds for postmenopausal breast cancer were elevated for: ever vs. never living with a smoking spouse (OR=1.32; 95% CI: 1.09, 1.60); consuming an average of 55+ vs. <55 servings per year of grilled/smoked meat (OR=1.52; 95% CI: 1.24, 1.87); ever vs. never residential use of synthetic logs (OR=1.44, 95% CI: 1.08, 1.92); and, perhaps, vehicular traffic exposure (OR=1.30, 95% CI: 0.85, 1.97). Active smoking (OR=1.00; 95% CI: 0.83, 1.21) and detectable PAH-DNA adducts (OR=1.10; 95% CI: 0.84, 1.44) were not associated with postmenopausal breast cancer. As shown in Table 2, effect measure modification by BMI was evident for the association between PAH-DNA adducts and postmenopausal breast cancer on the additive (ICR=0.49; 95% CI: 0.01, 0.96) and multiplicative (ROR=1.56; 95% CI: 0.91, 2.68) scales. The OR was elevated for the association between detectable vs. non-detectable adducts and postmenopausal breast cancer among women with BMI ≥25 kg/m^2 (OR=1.34; 95% CI: 0.94, 1.92), but not among those with a BMI <25 kg/m^2 (OR=0.86; 95% CI: 0.57, 1.28) (LRT p=0.1).

As also shown in Table 2, there was suggestive synergistic effect measure modification (additive and multiplicative) by BMI for the association for ETS from spouse and for grilled/smoked meat intake, but the estimates were imprecise. The OR for the association between ever ETS from spouse and postmenopausal breast cancer was only modestly elevated among women with a BMI <25 kg/m^2 (OR=1.19; 95% CI: 0.89, 1.59), but was stronger among those with a BMI ≥25 kg/m^2 (OR=1.43; 95% CI: 1.11, 1.83) (LRT p=0.3). Conversely, for synthetic log use there was evidence of antagonistic effect measure modification on the additive and multiplicative scales (ICR=−1.06, 95% CI: −2.09, −0.02; ROR=0.82; 95% CI: 0.28, 0.87, respectively). The stratified OR for those with a BMI ≥25 kg/m^2 was attenuated compared to those with a BMI <25 kg/m^2 (1.02 vs. 2.09). There was no evidence of either additive or multiplicative effect measure modification by BMI for either active smoking or vehicular traffic exposure (Table 2).

As shown in Table 3, suggestive effect measure modification by weight change was observed for the association between ETS from spouse and postmenopausal breast cancer on the additive (ICR=0.44; 95% CI: −0.10, 0.97) and multiplicative (ROR=1.38; 95% CI: 0.75, 2.53) scales. In the stratified analysis, the OR for the ETS-postmenopausal breast cancer association was elevated among women who gained weight (OR=1.41; 95% CI: 1.14, 1.73), but not among those who maintained weight (OR=1.02; 95% CI: 0.57, 1.80); the ROR was 1.38 (95% CI: 0.75, 2.53; LRT p=0.3). Similarly, ORs for postmenopausal breast cancer were higher in women who gained weight compared to those who maintained weight, for active smoking (1.06 vs. 0.82; ROR=1.29) and for PAH-DNA adducts (1.25 vs. 0.99; ROR=1.27), but the 95% confidence limits were imprecise (Table 3). No evidence of additive or multiplicative modification by weight change was found for grilled/smoked meat, synthetic log use, or vehicular traffic in association with postmenopausal breast cancer.

We also evaluated these associations with *in situ* cases excluded from the models. Point estimates generated by the models restricted to invasive cases only were not substantially different from those that included all cases, and interpretation of our results did not change (data not shown). However, the exclusion of *in situ* cases decreased our sample size of cases by 145 women and thus the corresponding confidence intervals were slightly wider.

In addition, because of potential selection bias concerns associated with blood donation, we constructed models for the PAH-DNA adducts using inverse probability weighting (using weights for factors associated with donating blood including age, race, education, alcohol use, and hormone replacement use (Gammon et al., 2002a)). The weighted results (data not shown) were nearly identical to the unweighted results shown in Tables 2 and 3.

Discussion

In this population-based case-control study, BMI was an effect modifier of the association between PAH-DNA adducts and postmenopausal breast cancer on the additive and multiplicative scales, with an increased OR observed among overweight/obese women, but not among the others. Also, there was some suggestion of modification by BMI for other PAH measures including ETS from spouse and grilled/smoked meat intake. In addition, among women who gained weight as an adult, the ORs were elevated for ETS from spouse and detectable PAH-DNA adducts in association with postmenopausal breast cancer, but not among those who maintained weight, suggesting effect modification on the multiplicative scale, although estimates were imprecise.

Despite the imprecision of some of the effect estimates due to small cell sizes, the majority of the point estimates were in the direction expected by the study hypothesis, such that women with higher BMI and women who gained weight had greater ORs than those with lower BMI or those who maintained weight, respectively. These findings support our hypothesis that individuals with more fat tissue may store and metabolize PAHs to a different extent than those with lesser amounts of body fat, which may result in chronic, long-term exposure to these lipophilic carcinogens.

In the study reported here, there was one exception to this general pattern of effect modification by body size. For synthetic log use there appeared to be an antagonistic modification by BMI for synthetic log use. The elevated association between synthetic log use and postmenopausal breast cancer in the BMI <25kg/m^2 stratum was actually attenuated in those with BMI ≥25 kg/m^2. There is not a strong biological rationale for why this could be the case, and thus it is plausible that this was a chance finding or perhaps could be due to another constituent in synthetic logs with an opposing mechanism of action. Another possible explanation is differential use of stoves/fireplaces and synthetic logs by individuals who are overweight/obese as compared with those who are not. It has been previously reported that greater body fat provides insulation from heat loss and higher metabolic heat production (Savastano et al., 2009), so perhaps those who are underweight/ideal weight use fireplaces for heating more than those who are overweight/obese. Among the postmenopausal women in the LIBCSP, 16% of those with BMI <25 kg/m^2 report ever burning synthetic logs compared to 11% with BMI ≥25 kg/m^2. However, the LIBCSP parent study did not assess frequency of use, and thus the study reported here could not evaluate whether those with BMI <25 kg/m^2 use synthetic logs more frequently (and thus have higher cumulative exposure) compared to those with BMI ≥25 kg/m^2.

The study reported here is the first to examine modification by BMI or weight change on the associations between multiple measures of PAHs and breast cancer incidence. One previous

study stratified associations between active smoking and postmenopausal breast cancer by obesity and waist circumference and reported that the association between active smoking was found in non-obese (defined as <30 kg/m^2), but not obese (> 30 kg/m^2) women (Luo et al., 2011a). Conversely, in our study there was no significant association with active smoking in either BMI group. Active smoking, in addition to being a source of carcinogenic PAHs, also demonstrates anti-estrogenic properties (Tanko and Christiansen, 2004). It is possible that in cigarette smoke where the apparent PAH exposure dose is usually stronger than in other PAH sources (Menzie et al., 1992) the two effects, carcinogenic and anti-estrogenic, on breast cancer risk may be counteracted (Hankinson et al., 2004). Also, results from previous studies do not suggest anti-estrogenic effects for passive smoke (Soldin et al., 2011), for which the apparent PAH exposure dose is less pronounced (Menzie et al., 1992) and for which we found potentially stronger evidence of modification by obesity status. It was a strength of our study to consider multiple sources of PAHs, as well as a biomarker of exposure.

In the study reported here, effect modification of the PAH-postmenopausal breast cancer association did not differ substantially by whether we considered adult BMI, a proxy measure of overall obesity, or weight change from age 20 to reference, a proxy measure of central adiposity (Svendsen et al., 1995). Although no other surrogate measures of obesity or measures of central adiposity, such as waist circumference, are available in the LIBCSP, both BMI and adult weight gain have each been consistently associated with postmenopausal breast cancer (Eng et al., 2005; Han et al., 2006; Keum et al., 2015; Lahmann et al., 2005; Morimoto et al., 2002). However, for some chronic diseases, central adiposity is more strongly associated with adverse health outcomes than BMI (Canoy, 2008; Després, 2012; Rosety-Rodriguez et al., 2013; Rothney et al., 2013). The results reported here suggest that when considering effect modification of the relationship between PAH and postmenopausal breast cancer, whether the body size measure reflects overall versus central adiposity may not matter.

A limitation of our study is that we were not able to examine the PAH-breast cancer associations among those who lost weight, due to the very small number of women in this weight change category. Also, as previously described (Eng et al., 2005), the risk estimates for postmenopausal breast cancer among those who lost weight differed from those who maintained weight over their lifetime; thus, to avoid bias, we did not collapse those who lost weight into the same weight change category as those who maintained their weight.

PAH-DNA adduct biomarkers are not subject to participant recall bias. However, factors associated with blood donation (Gammon et al., 2002a) could potentially bias our study findings. Nonetheless, our results essentially remained unchanged when we conducted inverse probability weighting, decreasing the concern that selection bias may have occurred from participants selecting to donate a blood sample.

For several other assessments used in the present study, women were asked to report exposures across decades of life. Recall of PAH sources from the distant past is a potential concern. Validity of recall specific to grilled/smoked meats has not previously been determined directly (Steck et al., 2007), but studies on the long-term recall of other

components of dietary intake have shown modest agreement between reports 11–24 years apart (Byers et al., 1983; Jensen et al., 1984; Lindsted and Kuzma, 1989; Sobell et al., 1989). Furthermore, if there is exposure misclassification, previous studies have reported that recall of diet is non-differential by breast cancer case/control status (Byers et al., 1983; Friedenreich et al., 1992; Lindsted and Kuzma, 1989). The grilled/smoked meat exposure in the present study was dichotomized; non-differential misclassification of an exposure with two levels would be expected to bias the results towards the null. For the other PAH variables used in the study reported here, other investigators have found that individuals are able to accurately recall if they had ever lived with a smoking spouse (Avila-Tang et al., 2013; Coultas et al., 1989) or ever smoked (Krall et al., 1989). No studies have evaluated the accuracy of self-reported material burned in stoves/fireplaces (White et al., 2014). BMI was derived from recalled body weight and height, which have been shown by others to be accurately and reliably recalled (Casey et al., 1991; Dahl and Reynolds, 2013; Kyulo et al., 2012; Norgan and Cameron, 2000; Troy et al., 1995).

PAH-DNA adducts are a pro-carcinogenic marker of recent exposure to PAHs. Since the other PAH measures considered occurred over long periods of time we are assuming, as in many environmental epidemiology studies, that current levels reflect past exposure. No biomarkers that assess long-term exposure to PAHs are available. Nonetheless, current adduct levels are still relevant, if the effects of PAHs are thought to be late-acting in the carcinogenic process, since they are not only initiators, but also promoters (Bostrom et al., 2002). PAH-DNA adducts also reflect an individual's susceptibility and ability to detoxify PAHs (Gammon and Santella, 2008; Santella et al., 1992). Therefore, a biomarker of recent exposure may represent how the body would have also responded to the exposure in the past (Gammon et al., 2004b). PAH biomarkers have been assessed using multiple assessment methods in various tissues, including blood (Gammon et al., 2004b; Gammon et al., 2002b; Saieva et al., 2011), tumor (Rundle et al., 2000a; Saieva et al., 2011; Santella et al., 2000), and urine (Lee et al., 2010), but currently there are no reports with multiple biomarkers assessed within the same individual.

With the exception of the biomarker PAH-DNA adducts, it is important to note that sources of PAHs were evaluated, rather than direct measures of individual PAHs. These sources contain other chemicals that can influence cancer risk. For example, grilled/smoked meat also contains heterocyclic aromatic amines (HAAs) (Knize et al., 1999); synthetic logs contain particulate matter, volatile organic compounds, nitrogen oxides, and polychlorinated biphenyls (Li and Rosenthal, 2006); cigarette smoke contains at least 60 carcinogens (Centers for Disease Control, 2010); and vehicular traffic contains benzene and formaldehyde (IARC, 2014). The variables that we considered are known to be the most important contributors of PAH exposure in the general population (Bostrom et al., 2002).

Additional strengths of this study include its population-based design, which improves study generalizability. Most LIBCSP participants are white, which is the subgroup which remains at highest risk of developing postmenopausal breast cancer in the U.S (Chlebowski et al., 2005). Thus, results reported here may not apply to black or Hispanic women. However, there is no reason to suspect that these biologic relationships would vary based on race or ethnicity. Further, in this study, we considered associations among women with *in situ* or

invasive breast cancer. Although clinically these tumors are treated differently in the clinic and have different prognoses, epidemiologically their very similar risk factor profiles (Kerlikowske, 2010) suggest that etiologically the two are very similar. Our findings, which showed that the point estimates from models restricted to women with invasive tumors were consistent with those that included all women, support this supposition.

In summary, in this population-based study, the OR for the association between PAH-DNA adducts and postmenopausal breast cancer incidence was increased among women who were overweight/obese, but not among the others. Similar patterns were observed for most other PAH measures and when weight gain was considered, but estimates were less precise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Examined whether obesity modifies associations between PAHs and breast cancer.
- PAH-DNA adducts more strongly associated with breast cancer if overweight or obese.
- There was suggestive modification by obesity for a few other measures of PAHs.
- Extent of modification was similar for BMI and weight gain.

Table 1

Odds ratios and 95% confidence intervals for the associations between PAH source/PAH-DNA adducts and postmenopausal breast cancer in the Long Island Breast Cancer Study Project (LIBCSP), 1996–1997

Exposure	Cases (N)	Controls (N)	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[a]
Active smoking				
Never	447	433	1.00	1.00
Ever	559	554	1.02 (0.85, 1.22)	1.00 (0.83, 1.21)
ETS from spouse				
Never	447	494	1.00	1.00
Ever	528	462	1.26 (1.05, 1.51)	1.32 (1.09, 1.60)
Grilled/smoked meat [b]				
0–54 servings	324	373	1.00	1.00
55+ servings	615	533	1.48 (1.22, 1.80)	1.52 (1.24, 1.87)
Synthetic log use				
Never	873	884	1.00	1.00
Ever	130	101	1.40 (1.06, 1.85)	1.44 (1.08, 1.92)
Vehicular traffic exposure				
<95th percentile	790	800	1.00	1.00
≥95th percentile	56	46	1.23 (0.92, 1.84)	1.30 (0.85, 1.97)
PAH-DNA adducts				
Non-detectable	155	172	1.00	1.00
Detectable	417	413	1.12 (0.86, 1.45)	1.10 (0.84, 1.44)

[a] Adjusted for age, alcohol intake, marital status, parity, education, and energy intake

[b] Average number servings per year and averaged over 6 decades of life (<20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, and 60+ years)

[c] Main effects in this study differ slightly from those published in previous LIBCSP studies (Gammon et al., 2004a; Gammon et al., 2004b; Mordukhovich et al., 2015; Steck et al., 2007; White et al., 2014) because we used different exposure categorizations and our ancillary study was restricted to postmenopausal women.

Table 2

Additive and multiplicative effect measure modification by BMI for the multivariable-adjusted[a] associations between PAH sources/PAH-DNA adducts and postmenopausal breast cancer, Long Island Breast Cancer Study Project, 1996–1997

BMI[b] (kg/m^2)	PAH exposure	Cases (N)	Controls (N)	Single referent ORs (95% CIs)	Additive ICR (95% CI)[c]	Stratified ORs (95% CIs)	Multiplicative ROR[d] (95% CI)	LRT[d] p- value
	Active smoking							
<25	Never	159	176	1.00		1.00		
	Ever	227	262	1.01 (0.76, 1.35)		1.01 (0.76, 1.35)		
≥25	Never	280	247	1.35 (0.99, 1.77)		1.00		
	Ever	324	282	1.32 (1.00, 1.75)	−0.01 (−0.45, 0.42)	1.00 (0.78, 1.27)	0.99 (0.68, 1.44)	0.9
	ETS from spouse							
<25	Never	175	209	1.00		1.00		
	Ever	197	217	1.19 (0.89, 1.59)		1.19 (0.89, 1.59)		
≥25	Never	269	274	1.22 (0.93, 1.60)		1.00		
	Ever	318	238	1.74 (1.31, 2.30)	0.33 (−0.13, 0.79)	1.43 (1.11, 1.83)	1.20 (0.82, 1.75)	0.3
	Grilled/smoked meat							
<25	0–54 servings	130	159	1.00		1.00		
	55+ servings	236	237	1.40 (1.03, 1.91)		1.40 (1.03, 1.91)		
≥25	0–54 servings	189	206	1.15 (0.84, 1.59)		1.00		
	55+ servings	371	287	1.87 (1.39, 2.51)	0.31 (−0.18, 0.80)	1.62 (1.24, 2.11)	1.15 (0.77, 1.72)	0.5
	Synthetic log use							
<25	Never	316	392	1.00		1.00		
	Ever	70	44	2.09 (1.38, 3.17)		2.09 (1.38, 3.17)		
≥25	Never	542	474	1.44 (1.17, 1.76)		1.00		
	Ever	59	55	1.87 (0.98, 2.21)	−1.06 (−2.09, − 0.02)	1.02 (0.69, 1.52)	0.49 (0.28, 0.87)	0.01
	Vehicular traffic							
<25	<95th percentile	290	356	1.00		1.00		
	≥ 95th percentile	25	21	1.44 (0.78, 2.67)		1.44 (0.78, 2.67)		
≥25	<95th percentile	487	428	1.39 (1.13, 1.72)		1.00		
	≥95th percentile	31	25	1.65 (0.93, 2.92)	−0.18 (−1.46, 1.09)	1.18 (0.67, 2.08)	0.82 (0.36, 1.89)	0.6
	PAH-DNA adducts							

BMI[b] (kg/m^2)	PAH exposure	Cases (N)	Controls (N)	Single referent ORs (95% CIs)	Additive ICR (95% CI)[c]	Stratified ORs (95% CIs)	Multiplicative ROR[d] (95% CI)	LRT[d] *p*- value
	Active smoking							
<25	Non- detectable	67	76	1.00		1.00		
	Detectable	156	196	0.86 (0.57, 1.28)		0.86 (0.57, 1.28)		
≥25	Non- detectable	86	91	1.02 (0.64, 1.61)		1.00		
	Detectable	257	213	1.36 (0.91, 2.01)	0.49 (0.01, 0.96)	1.34 (0.94, 1.92)	1.56 (0.91, 2.68)	0.1

[a]Adjusted for age, alcohol intake, marital status, parity, education, and energy intake

[b]BMI at reference

[c]ICR, interaction contrast ratio for additive interaction

[d]ROR, Ratio of odds ratios; LRT, likelihood ratio test for multiplicative interaction

Table 3

Additive and multiplicative effect measure modification by weight change (from age 20 to reference date[a]) for the multivariable-adjusted[b] associations between PAH sources/PAH-DNA adducts and postmenopausal breast cancer, LIBCSP, 1996–1997

Weight change[c]	PAH exposure	Cases (N)	Controls (N)	Single referent ORs (95% CIs)	Additive ICR (95% CI)[d]	Stratified ORs (95% CIs)	Multiplicative ROR (95% CI)	LRT[e] *p*- value
	Active smoking							
Maintain	Never	45	46	1.00		1.00		
	Ever	58	71	0.82 (0.47, 1.46)		0.82 (0.47, 1.46)		
Gain	Never	375	354	1.07 (0.67, 1.71)		1.00		
	Ever	472	439	1.14 (0.71, 1.81)	0.24 (−0.25, 0.74)	1.06 (0.86, 1.30)	1.29 (0.71, 2.35)	0.4
	ETS from spouse							
Maintain	Never	48	52	1.00		1.00		
	Ever	49	63	1.02 (0.57, 1.80)		1.02 (0.57, 1.80)		
Gain	Never	370	397	1.12 (0.72, 1.76)		1.00		
	Ever	454	370	1.58 (1.00, 2.48)	0.44 (−0.10, 0.97)	1.41 (1.14, 1.73)	1.38 (0.75, 2.53)	0.3
	Grilled/smoked meat							
Maintain	0–54 servings	34	43	1.00		1.00		
	55+ servings	62	68	1.42 (0.78, 2.60)		1.42 (0.78, 2.60)		
Gain	0–54 servings	272	292	1.31 (0.79, 2.19)		1.00		
	55+ servings	520	436	1.95 (1.17, 3.25)	0.22 (−0.50, 0.93)	1.49 (1.19, 1.86)	1.05 (0.55, 1.97)	0.9
	Synthetic log use							
Maintain	Never	90	107	1.00		1.00		
	Ever	13	12	1.42 (0.61, 3.34)		1.42 (0.61, 3.34)		
Gain	Never	731	707	1.27 (0.93, 1.75)		1.00		
	Ever	113	83	1.81 (1.19, 2.75)	0.11 (−1.17, 1.39)	1.42 (1.04, 1.94)	1.00 (0.40, 2.46)	1.0
	Vehicular traffic							
Maintain	<95th percentile	70	95	1.00		1.00		
	≥95th percentile	7	<5	NE[f]		NE		
Gain	<95th percentile	680	646	1.38 (0.98, 1.95)		1.00		
	≥95th percentile	44	37	1.66 (0.95, 2.89)	NE	1.20 (0.76, 1.91)	NE	NE
	PAH-DNA adducts							

Weight change[c]	PAH exposure	Cases (N)	Controls (N)	Single referent ORs (95% CIs)	Additive ICR (95% CI)[d]	Stratified ORs (95% CIs)	Multiplicative ROR (95% CI)	LRT[e] *p*- value
Maintain	Non- detectable	13	17	1.00		1.00		
	Detectable	46	50	0.99 (0.41, 2.36)		0.99 (0.41, 2.36)		
Gain	Non- detectable	131	146	1.02 (0.45, 2.28)		1.00		
	Detectable	358	330	1.27 (0.58, 2.78)	0.27 (−0.50, 1.03)	1.25 (0.93, 1.67)	1.27 (0.51, 3.17)	0.6

[a] Reference date: date of diagnosis for cases and date of identification for controls

[b] Adjusted for age, alcohol intake, marital status, parity, education, and energy intake

[c] Maintain: +/− 3kg; Gain: >3kg

[d] ICR, interaction contrast ratio for additive interaction

[e] ROR, Ratio of odds ratios; LRT, likelihood ratio test for multiplicative interaction

[f] NE, Not estimated due to less than 5 controls