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Polycyclic Aromatic Hydrocarbon-DNA Adducts and Survival among Women with Breast Cancer

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Abstract

Polycyclic aromatic hydrocarbons (PAH) are mammary carcinogens in animal studies, and a few epidemiologic studies have suggested a link between elevated levels of PAH-DNA adducts and breast cancer incidence. An association between PAH-DNA adducts and survival among breast cancer cases has not been previously reported. We conducted a survival analysis among women with newly diagnosed invasive breast cancer between 1996 and 1997, enrolled in the Long Island Breast Cancer Study Project. DNA was isolated from blood samples that were obtained from cases shortly after diagnosis and before treatment, and assayed for PAH-DNA adducts using an ELISA. Among the 722 cases with PAH-DNA adduct measurements, 97 deaths (13.4%) from all causes and 54 deaths (7.5%) due to breast cancer were reported to the National Death Index (NDI) by December 31, 2002. Using Cox proportional hazards models and controlling for age at diagnosis, we did not find evidence that all-cause mortality (hazard ratio (HR) = 0.88; 95% confidence interval (CI): 0.57–1.37), or breast cancer mortality (HR = 1.20; 95% CI: 0.63–2.28) was strongly associated with detectable PAH-DNA adduct levels compared with non-detectable adducts; additionally, no dose-response association was observed. Among a subgroup with treatment data (n=520), adducts were associated with over a two-fold higher mortality among those receiving radiation, but mortality for adducts was reduced among hormone therapy users. Results from this large population-based study do not provide strong support

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for an association between detectable PAH-DNA adducts and survival among women with breast cancer, except perhaps among those receiving radiation treatment.

Keywords

breast neoplasms; mortality; survival analysis; polycyclic aromatic hydrocarbons; environmental health

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous environmental compounds formed from incomplete combustion of carbon-containing materials, including coal, gas and cigarette smoke. PAH exposure routes include inhalation, ingestion of PAH-containing food (e.g., grilled/smoked foods), and dermal absorption. Binding of PAH with DNA and consequent adduct formation provide an opportunity for measuring body burden in human tissue (Santella et al., 1999).

Several epidemiologic studies report an association between PAH-DNA adducts and breast cancer incidence (Gammon et al., 2004; Gammon et al., 2002a; Li et al., 1996; Rundle et al., 2000). In the Long Island Breast Cancer Study Project (LIBCSP) case-control analysis we found a positive association between PAH-DNA adducts and breast cancer incidence (OR=1.29, 95% CI: 1.05, 1.58) (Gammon et al., 2004). To date no studies have reported the association between PAH-DNA adducts and survival.

We conducted a follow-up study to investigate the association between PAH-DNA adducts and mortality due to all causes and to breast cancer-specific causes among the cohort of cases participating in the LIBCSP (Gammon et al., 2002b).

METHODS

Study Population

For the parent LIBCSP case-control study (Gammon et al., 2002b) cases included 1,508 (82% of eligible cases) English-speaking women residing in Nassau or Suffolk county on Long Island, NY with newly diagnosed first primary breast cancer between August 1, 1996, and July 31, 1997. Cases ranged in age from 20 to 98 years at diagnosis, 94% are white, 4% are African American, and 2% are of other race. Our analyses are restricted to cases with invasive breast cancer (n=1,273).

The baseline, case-control questionnaire (Gammon et al., 2002b) was administered in-person shortly after diagnosis and assessed demographic characteristics; medical history (including family history of breast cancer); body size; physical activity; menstrual and reproductive histories; exogenous hormone use; active and passive cigarette smoking; and alcohol consumption. Medical records were abstracted for tumor characteristics including estrogen/progesterone receptor (ER/PR) status.

Exposure Assessment and Laboratory Methods

Non-fasting blood samples of sufficient volume were collected from 722 invasive breast cancer cases before treatment was administered and PAH-DNA adducts assayed using a competitive ELISA. Laboratory methods were described previously (Gammon et al., 2004; Gammon et al., 2002a). Briefly, two rounds of samples were run by the same laboratory (RMS) using the same procedures and later pooled. PAH diol epoxide-DNA adducts were analyzed by competitive ELISA using a method that has been described (Poirier et al., 1980; Santella et al., 1992). For

analytical purposes, those samples with <15% inhibition were considered non-detectable and assigned a value of $1/10^8$, an amount midway between the lowest positive value and zero. For Round 1 a positive control run with multiple batches of samples (n = 11) had a mean (±SD) of 20.3 (±5.0) with a CV of 25%. For Round 2 the mean value and standard deviation (SD) for the positive control run with multiple batches was 7.8 (3.10)(n = 10). As an additional quality control measure, samples were assayed in duplicate (10% for Round 1 and 17% for Round 2); there was no significant difference in mean adduct levels (Round 1: mean difference = −0.60 (SD = 2.43); $P = 0.60$ by paired t test; Round 2: mean difference = −0.02 (SD = 3.24), paired t-test p-value = 0.93).

Outcome Assessment

For the follow-up study (Sagiv et al., 2007), National Death Index (NDI) data were linked during the period beginning with the date of diagnosis until December 31, 2002. Median duration of follow-up for the 722 cases was 70.6 months (range, 4.6 – 88.6 months). Among 722 women with invasive breast cancer, there were 97 deaths (13.4%) due to all causes, of which 54 deaths (7.5%) were due to breast cancer. Complete treatment regimen for the initial breast cancer diagnosis was obtained by re-contacting case women (or proxy) and retrieving and abstracting updated medical records (Sagiv et al., 2007). Among women with complete medical records (n=520), concordance of treatment information based on abstracted medical records and self-reported treatment was high (kappa = 0.97 for radiation therapy, 0.96 for chemotherapy, and 0.92 for hormone therapy), and thus the self-reported data are used in the analysis reported here. Data on complete course of treatment is available for 520 cases.

Statistical Analysis

PAH-DNA adduct levels were log transformed and analyzed as a binary variable (detectable/not-detectable) and using quintiles with non-detectable adduct levels in the lowest quintile and then dividing the remaining subjects with detectable adducts into quartiles. For the all-cause mortality analysis, events (failures) were all deaths between the date of diagnosis and the end of follow-up (December 31, 2002). Participants that did not die before the end of follow-up were censored at the end of follow-up. For breast cancer-specific mortality, events were all deaths due to breast cancer between the date of diagnosis and the end of follow-up. Participants that died of any other cause before the end of follow-up were censored at their date of death, and participants that did not die before the end of follow-up were censored at the end of follow-up.

Hazard ratios (HR) and 95% confidence intervals (CI) were estimated with Cox proportional hazards models (Allison, 1995), adjusting for covariates described previously (Gammon et al., 2002b; Gaudet et al., 2004; Shantakumar et al. 2005). Violation of the proportional hazards assumption was examined for exposure and covariates using log (−log) plots and by inclusion of a time-dependent interaction variable in the model. Potential confounders evaluated included age at diagnosis, race and ethnicity, religion, education, household income, marital status, length of residence in interview home, benign breast disease, family history of breast cancer, BMI (weight in kilograms/height in meters squared) at reference, age at menarche, hormone replacement use, menopausal status at diagnosis, oral contraceptive use, age at first birth, parity, lactation history, history of fertility problems, mammography, active and passive cigarette smoking, alcohol consumption, dietary intake of grilled and smoked food, fruits and vegetables and total dietary benzo[a]pyrene intake. Definitions of these covariates were previously described (Gammon et al., 2002b; Gaudet et al., 2004; Shantakumar et al. 2005). Covariates were retained in the final model if their inclusion in the multivariable model changed the HR by more than 10% (Rothman and Greenland, 2005). Effect modification between PAH-DNA adducts and mortality was assessed for age, ER/PR receptor status, menopausal status, body mass index (BMI), tobacco and alcohol use. Interaction terms were added to the Cox models

to estimate HRs across each level of these modifiers and effect modification was assessed statistically with the likelihood ratio test (Allison, 1995). We also explored possible effect modification by treatment (radiation, chemotherapy and hormone therapy).

RESULTS

None of the covariates changed the HR by more than 10% and thus only unadjusted and age-adjusted estimates are presented. We observed a 20% increase in the HR for the association between detectable PAH-DNA adducts and breast cancer-specific mortality (age-adjusted HR=1.20, 95% CI: 0.63, 2.28), but the estimate was not statistically significant. In contrast, for all-cause mortality, we observed a very modest non-statistically significant inverse association with detectable adduct levels (age-adjusted HR=0.88, 95% CI: 0.57, 1.37); quintile analyses also showed this inverse pattern, though estimates were imprecise (Table 1).

There was a suggestion of effect modification for all-cause and breast cancer-specific mortality by several modifiers (Table 2), with higher mortality risk among cases with hormone receptor negative tumors (ER−/PR−), premenopausal cases, overweight cases, non-smokers and those exposed to passive cigarette smoke, and alcohol consumers; none of these interactions were statistically significant, however.

Among the subgroup with information available on complete course of treatment received for the initial breast cancer (n=520), cases that received radiation therapy had higher PAH-DNA adduct associations with all-cause and breast cancer-specific mortality (age-adjusted HR =2.47, 95% CI: 0.74, 8.21, likelihood ratio p-value=0.21 and HR=5.94, 95% CI: 0.80, 44.38, likelihood ratio p-value<0.01, respectively). In contrast, cases that received hormone therapy had lower PAH-DNA adduct associations with all-cause and breast cancer mortality (age-adjusted HR =0.52, 95% CI: 0.24, 1.13, likelihood ratio p-value=0.01 and HR=0.67, 95% CI: 0.25, 1.78, likelihood ratio p-value=0.07, respectively). There was no observed effect modification between PAH-DNA adducts and mortality by chemotherapy.

DISCUSSION

We did not observe strong associations between PAH-DNA adducts and all-cause or breast cancer mortality among the LIBCSP cases. There was little evidence for effect modification of these associations by age at diagnosis, hormone receptor status, menopausal status, BMI, cigarette smoke or alcohol consumption. Associations were modified by treatment, however, with more than a doubling in risk of mortality associated with detectable PAH-DNA adducts among the subgroup who received radiation therapy, but a lower mortality risk due to adducts among hormone therapy users.

Important predictors of breast cancer survival reported in the literature include stage at diagnosis and treatment (American Cancer Society, 2004; Chu et al. 1996), with consistent associations also found for BMI (Tretli et al., 1990; Zhang et al., 1995). To our knowledge, this is the first study to look at the association between PAH-DNA adducts and mortality among breast cancer cases. Studies of diet (Zhang et al., 1995; Holmes et al., 1999; Newman et al., 1986), exogenous hormone use (Holmberg et al., 1994; Reeves et al. 2000), reproductive history (Daling et al., 2002; Whiteman et al., 2004), physical activity (Holmes et al., 2005; Rohan et al., 1995) and alcohol consumption (Ewertz et al., 1994; McDonald et al., 2002) are less conclusive. Though there has been concern that cigarette smoking among women with breast cancer is associated with survival (Ewertz et al., 1994; Manjer et al., 2000; Vatten et al., 1991; Yu et al., 1997), we did not find this to be the case in our study (Sagiv et al., 2007). A significant strength of the current study is that exposure was based on PAH-DNA adducts, a biomarker of exposure, rather exposure based on self-report, as is the case with cigarette

smoking. Adduct levels reflect not only exposure dose but the body's response to the exposure and is therefore a better measure of body burden (Santella et al. 1999). Further, in a previous report of the Long Island Breast Cancer Study (Shantakumar et al. 2005), we found that women with higher adduct levels were more likely to be current or past smokers (OR=1.50, 95% CI=1.00, 2.24; OR=1.46, 95% CI=1.05, 2.02, respectively) and to have donated blood in summer and fall (OR=2.65, 95% C =1.69, 4.17; OR=1.59, 95% CI=1.08, 2.32, respectively). However, PAH from other sources, including food (estimated using a food frequency questionnaire and self-reports about intake of grilled and smoked foods) and vehicular traffic (estimated using geographic modeling techniques) were not associated with PAH-DNA adducts in these data.

The biologic mechanism for the association between PAH-DNA adducts and breast cancer mortality and the critical window for exposure to factors that lead to PAH-DNA adduct formation is unclear. PAHs, such as benzo(a)pyrene (BaP) and 7,12-dimethylbenz(a) anthracene (DMBA), are well known complete carcinogens, capable of both tumor initiation via genotoxic actions on DNA as well as tumor promotion through non-genotoxic signaling pathways (Luch, 2005). Thus, it is plausible that PAH exposure could act as a tumor promoter of cancer cells that eluded eradication during treatment, to increase the risk of tumor progression and hence mortality among breast cancer survivors.

Care was also taken to draw blood prior to treatment. The LIBCSP is the largest, most comprehensive study to date to investigate PAH-DNA adducts and breast cancer. Despite the large sample size, however, this study still had limited power to study mortality, most likely due to the small number of deaths that occurred over the study period. This was a particular problem when investigating effect modification as cell sizes were quite small. Treatment data were available for only a subset of breast cancer cases. This limited study power but probably did not result in a selection bias since the DNA-PAH adduct-mortality associations remained the same for the subgroup. Despite power limitations, if a true association between PAH-DNA adducts and mortality does exist, it is unlikely that this association is strong. Further investigation is warranted among a larger population with more outcomes, however, particularly among premenopausal women where PAH-related mortality may be higher.

In contrast to several other investigations (Ford et al., 2003; Neugut et al., 1994), we previously reported little evidence for an interaction between radiation treatment and smoking on mortality among women with breast cancer (Sagiv et al., 2007). The current analysis detected a two- to six-fold increase in mortality for the interaction between radiation therapy and detectable PAH-DNA adducts. Because the PAH biomarker is a measure of exposure as well as the inherent individual variability in response to the exposure (Santella et al., 1999), our biomarker results may identify those who are particularly susceptible to the dual effects of both PAH and radiation. Another explanation for this finding is that treatment is a reflection of disease stage, which in turn is a major predictor of survival. Thus, this potential interaction requires further evaluation in biomarker studies that include larger numbers of breast cancer survivors with information of stage over a longer period of follow-up.

In summary, these data do not support a strong association between PAH-DNA adducts and all cause or breast cancer mortality, though effect modification by treatment was observed. Investigation of modifiable environmental risk factors for breast cancer incidence and mortality remains a public health priority.

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Abbreviations

BMI
Body Mass Index

CI
Confidence Interval

DNA
Deoxyribonucleic acid

ER
Estrogen Receptor

HR
Hazard Ratio

LIBCSP
Long Island Breast Cancer Study Project

NDI
National Death Index

PAH
Polycyclic Aromatic Hydrocarbons

PR
Progesterone Receptor

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TABLE 1

Unadjusted and age-adjusted Cox regression hazard ratios of all-cause mortality and breast cancer mortality and PAH adduct level among invasive breast cancer cases diagnosed between August 1, 1996 and July 31, 1997 (n=722) and followed-up through December 31, 2002, participating in the Long Island Breast Cancer Study Project

	All Cause Mortality (n=97 deaths)				Breast Cancer Mortality* (n=54 deaths)			
	No. Deaths (%)	No. Censored	Unadjusted HR† (95% CI)	Age-adjusted HR† (95% CI)	No. Deaths (%)	No. Censored	Unadjusted HR† (95% CI)	Age-adjusted HR† (95% CI)
Detectable PAH-DNA adduct level								
No	28 (15.0)	159	1 Referent	1 Referent	12 (6.4)	175	1 Referent	1
Yes	69 (12.9)	466	0.86 (0.55–1.33)	0.88 (0.57–1.37)	42 (7.9)	493	1.21 (0.64–2.30)	1.20 (0.63–2.28)
Quintile of PAH-DNA adduct level								
1	28 (15.0)	159	1 Referent	1 Referent	12 (6.4)	175	1 Referent	1
2	19 (14.2)	115	0.95 (0.53–1.69)	1.02 (0.57–1.84)	12 (9.0)	122	1.39 (0.63–3.10)	1.37 (0.61–3.05)
3	19 (14.2)	115	0.95 (0.53–1.70)	0.99 (0.55–1.77)	10 (7.5)	124	1.16 (0.50–2.69)	1.15 (0.50–2.67)
4	15 (11.2)	119	0.74 (0.39–1.38)	0.73 (0.39–1.36)	9 (6.7)	125	1.03 (0.43–2.44)	1.03 (0.43–2.44)
5	16 (12.0)	117	0.80 (0.43–1.47)	0.82 (0.44–1.52)	11 (8.3)	122	1. 7 (0.56–22.88)	1.26 (0.56–2.86)

*Breast cancer reported as underlying cause of death

†Age-adjusted hazard ratio

TABLE 2

Effect modification of adjusted Cox regression hazard ratios of age-adjusted all-cause mortality and breast cancer mortality by age at diagnosis, hormone receptor status, menopausal status and BMI for detectable PAH adduct level among invasive breast cancer cases diagnosed between August 1, 1996 and July 31, 1997 (n=722) and followed-up through December 31, 2002, participating in the Long Island Breast Cancer Study Project

	All Cause Mortality (n=97 deaths)						Breast Cancer Mortality* (n=54 deaths)					
	Non-detects		Detectable adducts				Non-detects		Detectable adducts			
Stratifying Factor	No. Deaths (%)	No. Censored	No. Deaths (%)	No. Censored	Age-adjusted HR† (95% CI)	p‡	No. Deaths (%)	No. Censored	No. Deaths (%)	No. Censored	Age-adjusted HR† (95% CI)	p‡
Age at Diagnosis												
< 65 yr	13 (11.4)	101	37 (10.4)	319	1.01 (0.54–1.89)	0.71	8 (7.5)	106	30 (8.4)	326	1.34 (0.62–2.90)	0.85
65+ yr	15 (20.5)	58	32 (17.9)	147	0.86 (0.48–1.55)		4 (5.8)	69	12 (6.7)	167	1.17 (0.38–3.63)	
Hormone receptor status												
ER+/PR+	8 (9.4)	77	17 (6.7)	236	0.76 (0.33–1.76)	0.88	2 (2.4)	83	9 (3.6)	244	1.51 (0.33–7.02)	0.75
ER+/PR−	5 (25.0)	15	12 (21.4)	44	0.78 (0.27–2.22)		2 (10.0)	18	4 (7.1)	52	0.69 (0.13–3.77)	
ER−/PR+	1 (16.7)	5	2 (10.0)	18	0.72 (0.07–7.91)		1 (16.7)	5	2 (10.0)	18	0.72 (0.07–7.92)	
ER−/PR−	6 (22.2)	21	21 (27.6)	55	1.21 (0.49–2.99)		3 (11.1)	24	17 (22.4)	59	1.99 (0.58–6.79)	
Unknown	8	41	17	113			4	45	10	120		
Menopausal Status												
Premenopausal	5 (9.3)	49	20 (11.9)	148	1.51 (0.57–4.01)	0.22	4 (7.4)	50	16 (9.5)	152	1.53 (0.52–4.55)	0.65
Postmenopausal	23 (17.4)	109	46 (13.2)	303	0.78 (0.48–1.27)		8 (6.1)	124	24 (6.9)	325	1.13 (0.51–2.51)	
Unknown		1	3	15				1	2	16		
BMI												
Normal (<25)	12 (13.8)	75	21 (8.8)	218	0.68 (0.35–1.35)	0.41	6 (6.9)	81	12 (5.0)	227	0.76 (0.28–2.02)	0.41
Overweight (25–29.9)	6 (11.1)	48	24 (13.9)	149	1.44 (0.59–3.51)		2 (3.7)	52	13 (7.5)	160	2.26 (0.52–9.88)	
Obese (30+)	10 (21.7)	36	24 (19.5)	99	0.91) (0.44–1.89		4 (8.7)	42	17 (13.8)	106	1.51 (0.51–4.49)	
Active Cigarette Smoking												
Never	11 (12.5)	77	32 (14.0)	197	1.26 (0.64–2.48)	0.37	4 (4.5)	84	21 (9.2)	208	2.18 (0.76–6.32)	0.43
Former	7 (12.3)	50	21 (10.9)	172	0.98 (0.42–2.30)		3 (5.3)	54	9 (4.7)	184	0.89 (0.24–3.28)	
Current	10 (23.8)	32	16 (14.2)	97	0.61 (0.28–1.30)		5 (11.9)	37	12 (10.6)	101	0.94 (0.33–2.67)	
Active/Passive Cigarette Smoking												
Neither	3 (12.5)	21	4 (10.8)	37	0.96 (0.21–4.28)	0.33	2 (8.3)	22	2 (5.4)	35	0.66 (0.09–4.68)	0.24
Ever passive only	7 (11.3)	55	27 (14.5)	159	1.44 (0.63–3.29)		2 (3.2)	60	18 (9.7)	168	3.29 (0.77–14.09)	

	All Cause Mortality (n=97 deaths)						Breast Cancer Mortality* (n=54 deaths)					
	Non-detects		Detectable adducts				Non-detects		Detectable adducts			
Stratifying Factor	**No. Deaths (%)**	**No. Censored**	**No. Deaths (%)**	**No. Censored**	**Age-adjusted HR† (95% CI)**	**p‡**	**No. Deaths (%)**	**No. Censored**	**No. Deaths (%)**	**No. Censored**	**Age-adjusted HR† (95% CI)**	**p‡**
Ever active only	3 (30.0)	7	7 (16.3)	36	0.40 (0.12–1.38)		1 (10.0)	9	4 (9.3)	39	1.02 (0.11–9.14)	
Ever both	14 (16.3)	72	26 (10.2)	230	0.70 (0.37–1.34)		7 (8.1)	79	14 (5.5)	242	0.68 (0.27–1.68)	
Unknown	1	4	5	8				5	4	9		
Alcohol Consumption												
Never	13 (18.8)	56	21 (11.4)	164	0.63 (0.32–1.25)	0.18	7 (10.1)	62	14 (7.6)	171	0.74 (0.31–1.83)	0.12
Ever	15 (12.7)	103	48 (13.7)	302	1.17 (0.67–2.04)		5 (4.2)	113	28 (8.0)	322	2.04 (0.79–5.26)	

*Breast cancer reported as underlying cause of death

†Age-adjusted hazard ratio

‡Interaction p-value based on likelihood ratio test.