Breast Cancer Risk and Exposure in Early Life to Polycyclic Aromatic Hydrocarbons Using Total Suspended Particulates as a Proxy Measure

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Abstract

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous in the environment. We hypothesized that early life exposure to PAHs may have particular importance in the etiology of breast cancer. We conducted a population-based, case-control study of ambient exposure to PAHs in early life in relation to the risk of breast cancer. Total suspended particulates (TSP), a measure of ambient air pollution, was used as a proxy for PAHs exposure. Cases (n = 1,166) were women with histologically confirmed, primary, incident breast cancer. Controls (n = 2,105) were frequency matched by age, race, and county of residence to cases. Annual average TSP concentrations (1959-1997) by location were obtained from the New York State Department of Environmental Conservation for Erie and Niagara Counties. Based on the monitor readings, prediction maps of TSP concentrations were generated with ArcGIS 8.0 (ESRI, Inc., Redlands, CA) using inverse distance squared weighted interpolation. Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals. In postmenopausal women, exposure to high concentrations of TSP (>140 μg/m^3) at birth was associated with an adjusted odds ratio of 2.42 (95% confidence interval, 0.97-6.09) compared with exposure to low concentrations (<84 μg/m^3). However, in premenopausal women, where exposures were generally lower, the results were inconsistent with our hypothesis and in some instances were suggestive of a reduction in the risk of breast cancer. Our study suggests that exposure in early life to high levels of PAHs may increase the risk of postmenopausal breast cancer; however, other confounders related to geography cannot be ruled out. (Cancer Epidemiol Biomarkers Prev 2005;14(1):53–60)

Introduction

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous in the environment and commonly present in particulate air pollution (1, 2). PAHs are a broad category of chemical compounds composed of carbon and hydrogen and are formed as a byproduct during combustion of organic material. Important sources of PAHs include cigarette smoke, steel mills, foundries, automobiles, coal combustion for electricity production and many other industrial and nonindustrial processes. PAHs are also found in food and are formed when food is cooked at high temperatures (i.e., grilling meats). In addition to anthropogenic sources, natural sources (i.e., volcanoes and forest fires) also contribute PAHs to the atmosphere (1, 3). Most of these sources not only contribute to the release of PAHs into the environment, but also contribute to particulate air pollution. Ninety to 95% of particulate phase PAHs are physically associated with particulate matter <3.3 μm (2, 4). These small particles are thought to have particular biological relevance because they can be inhaled and deposited in the lower respiratory tract (5). PAHs are lipophilic (6, 7), have been shown to be mammary carcinogens in animal models (1, 8, 9), and there is evidence that they may also be human mammary carcinogens (10, 11). In addition, PAHs may also have estrogenic and antiestrogenic properties that could potentially affect breast cancer risk (12).

To our knowledge, no studies have examined exposure to total suspended particulates (TSP) and breast cancer risk and only a few epidemiologic investigations of breast cancer have examined PAHs. Petralia et al. (13) examined premenopausal breast cancer and occupational exposure to benzene and PAHs using job exposure matrices in a population-based, case-control study. High probability of occupational exposure to benzene and PAHs was associated with premenopausal breast cancer. However, because women were exposed to a mixture of compounds, the independent effect of PAHs was difficult to estimate.

Rundle et al. (11) examined PAH-DNA adducts in breast tumor tissue. They found a 2-fold increase in PAH-DNA adducts in malignant tumors compared with tissue from controls with benign breast disease with atypia. Gammon et al. (10) examined PAH-DNA adducts in mononuclear cells in relation to the risk of breast cancer in a case-control study of Long Island residents. They found a nearly 50% increase in the risk of breast cancer for subjects in the highest quintile of PAH-DNA adducts in mononuclear cells; there was no dose-response relationship.

Early life exposures, including exposure to PAHs, may have particular importance in the etiology of breast cancer (14). Early age at exposure to ionizing radiation, for example, confers increased risk of breast cancer when compared with later age at exposure (15, 16). In addition, several other established risk factors also indicate the importance of early life factors in the etiology of breast cancer. Breast cancer risk is increased in women with earlier age at menarche, whereas earlier age at first birth reduces the risk of breast cancer. The physiologic changes that occur to breast tissue during development further support the postulation that early life exposures may be important. Around menarche, the mammary gland begins to develop and

Received 5/6/04; revised 7/6/04; accepted 7/19/04.

Grant support: National Cancer Institute grant CA-09051 and NIH grants 5 R21CA8713802, DAMD-170010417, and ES 09816.

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differentiate into defined ducts and lobules. The primary lobules formed at this time are type 1 lobules. These lobules further differentiate into type 2 and type 3 lobules during pregnancy (17). *In vitro* studies have shown that cells from type 1 lobules are more sensitive to proliferation signals than either cells from type 2 or 3 lobules (18). In addition, human breast epithelial cells from type 1 lobules were more sensitive to the transforming effects of the PAH, 7,12-dimethlybenzo(a)anthracene and *N*-methyl-*N*-nitrosourea than were type 3 lobule cells (19).

We conducted a population-based, case-control study of exposure to PAHs in early life in relation to the risk of breast cancer using TSP, a measure of ambient air pollution, as a proxy for PAHs exposure. We examined time periods that are thought to be critical exposure periods with regard to susceptibility to breast cancer: at the time of birth, at menarche, at the time when the participant first gave birth, and 20 and 10 years before interview.

Materials and Methods

The Western New York Exposures and Breast Cancer Study (WEB Study) is a population-based, case-control study conducted with women living in Erie and Niagara Counties in Western New York State during 1996-2001. All participants were aged 35-79 years. Cases included 1,166 women with histologically confirmed, primary, incident breast cancer. In addition, cases under the age of 65 years were restricted to women with a driver's license. Controls (n = 2,105) were frequency matched by age, race, and county of residence to cases. Controls under the age of 65 years were randomly selected from the New York State Department of Motor Vehicles driver's license list and controls 65 years of age and over were randomly selected from the Centers for Medicare and Medicaid Services rolls. For these analyses, cases and controls were restricted to participants who were residents of Erie and Niagara Counties during each of the three pertinent time periods: birth, menarche, and first birth. A total of 1,638 cases and 3,396 controls met our inclusion criteria of between 35 and 79 years of age, current resident of Erie or Niagara County, no previous cancer diagnosis other than nonmelanoma skin cancer and an ability to speak English. The response rates were 71% (1,166 of 1,638) and 62% (2,105 of 3,396) for cases and controls, respectively. All participants provided informed consent; the protocol was approved by the Institutional Review Boards of the University at Buffalo School of Medicine and Biomedical Sciences and of participating hospitals.

Data Collection. Using extensive in-person interviews and self-administered questionnaires, participants provided information regarding medical history, diet, alcohol consumption, smoking history, lifetime passive smoke exposure, occupational history, and residential history. Residential histories were reported by the subject dating back to birth. For addresses in Erie and Niagara Counties, Polk and city directories were searched to find missing address information. For addresses with missing zip codes, we used ZP4 (Semaphore Co., Aptos, CA), a commercially available database that uses information about street name and number and city designation to find missing zip codes. Residential histories and interview data were used to identify each subject's residence at her birth, menarche, and her first birth. These addresses were geocoded with ArcView 3.2 (ESRI, Inc., Redlands, CA) using Dynamap 2000 (GDT, Inc., Lebanon, NH) as the reference theme (i.e., street map) of Erie and Niagara Counties. A previously published validation study found good agreement between global positioning system measurements of latitude and longitude and estimates of latitude and longitude from the geocoded addresses in Erie and Niagara Counties (20).

Exposure Assessment. The New York State Department of Environmental Conservation maintains air monitors that began measuring TSP in 1959. These monitors measured TSP concentrations every 7 days. Annual average TSP concentrations (1959-1997) were obtained from these monitors for Erie and Niagara Counties. In total, 87 monitors were operating at various times in Erie and Niagara Counties. For the period of the 1960s, there were fewer monitors operating than at later time periods. There was very little within monitor variation of TSP concentration during this time period and average TSP concentrations were calculated for the entire decade for each monitor. By averaging the TSP concentrations for each monitor, the overall TSP estimates were more stable. Considerably more monitors were operating in the years after 1969. Annual average TSP concentrations were calculated for each year for 1970 through 1997 for each monitor. In addition to TSP, ambient benzo(a)pyrene was measured between November 1, 1973 and November 1, 1974 in Erie County, NY for 11 of the 87 monitoring sites. The Pearson correlation coefficient between the measured log transformed TSP and log transformed benzo(a)pyrene concentrations at these 11 monitoring sites was 0.90, suggesting that the ambient TSP concentrations reasonably estimate ambient PAHs concentrations in this region.

Based on the monitor readings for each time period, prediction maps of TSP concentrations were generated with ArcGIS 8.0 (ESRI) using inverse distance squared weighed interpolation. We assumed a 45-degree angle to account for the prevailing southwesterly winds and limited the exposure estimation for each address to the seven closest sampling monitors. The primary assumption of these geostatistical methods is that close locations are more similar to one another than are locations relatively farther away (21). The estimated individual residential TSP concentrations were insensitive to changing the number of monitors included for the exposure estimation. In total, 29 prediction maps were constructed of estimated TSP concentrations for the two-county region; one for the 1960s and one for each year after that until 1997. These maps were used to determine exposure to TSP at each participant's address for the relevant time period. The 1960s TSP concentration prediction map is provided as an example in Fig. 1.

TSP concentrations for addresses before the 1960s were estimated assuming that the interpolated concentrations in the 1960s were representative of earlier time periods. Industrialization in Erie and Niagara Counties began at the end of the 19th century and the industrial activities that contributed most heavily to air pollution were very active before the 1960s and was relatively constant over the time period (22). Furthermore, measures to control air quality were not implemented until the early 1970s. Consequently, the 1960s concentrations of TSP probably reflect ambient levels in the earlier time period.

Statistical Analysis. Unconditional logistic regression (23) was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). TSP concentrations were categorized into four levels (<84, 84-114, 115-140, and >140 $\mu g/m^3$). The cut points for the categorical analyses were derived from the quartiles of the distribution of measurements of TSP concentrations in the 1960s. In addition to the categorical analysis, we examined TSP concentrations on a continuous scale. Furthermore, logistic quadratic spline regression with knots at 84 and 140 $\mu g/m^3$ was used to graphically depict the exposure-response trend; the estimated probability of being a case was calculated from the quadratic spline regression equation and adjusted for age, education and parity. The values for the two knots in the spline regression were selected based on the previous categorical analysis. The end categories were restricted to linear segments to prevent instability (24).

We considered age, race, education, age at first birth, age at menarche, parity, previous benign breast disease, family history of breast cancer, body mass index [weight (kg)/height

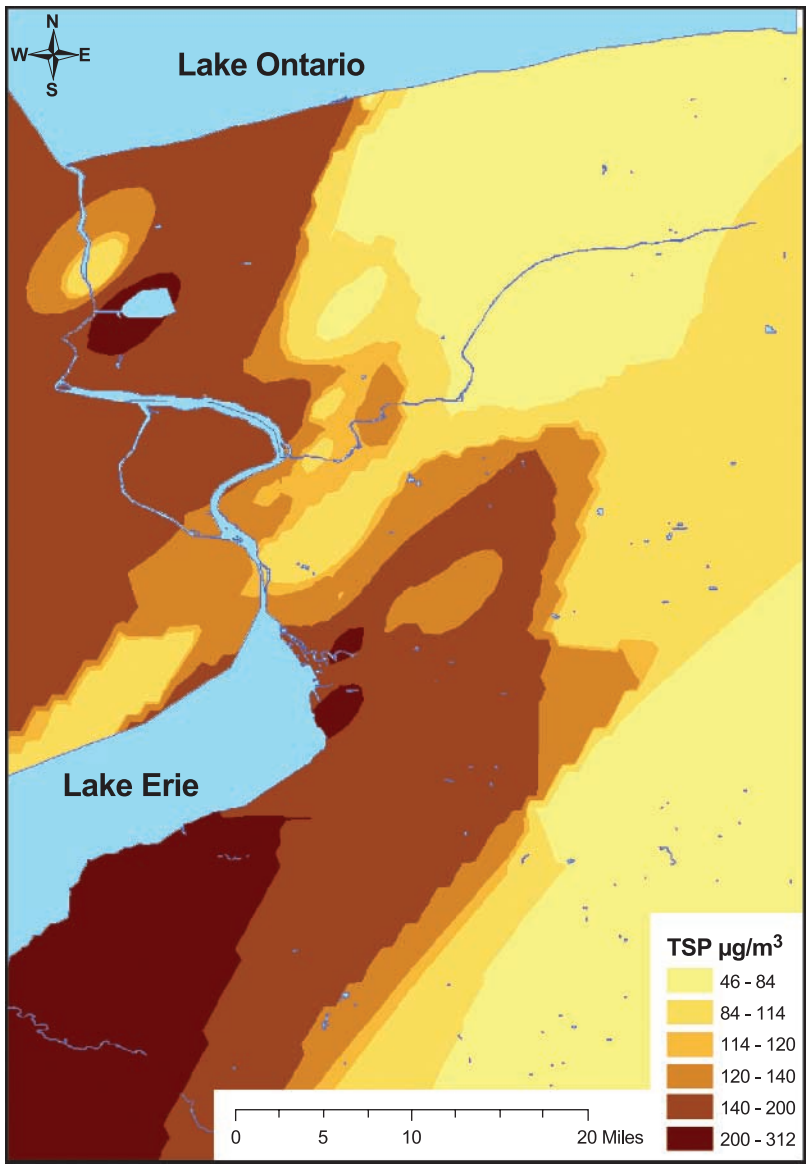

Figure 1. TSP concentrations in Erie and Niagara counties, Western New York (1960s).

$(m)^2$], and age at menopause as potential confounders in multivariate logistic regression. The model presented includes age, education, and parity and was determined by excluding variables from the full model which did not alter the risk estimates more than 10%. All models were stratified by menopausal status. *P* for trend statistics was determined by the *P* for the coefficient of the continuous exposure variable, while adjusting for covariates.

In addition to the time period–specific analyses, cumulative exposure was assessed by calculating the cumulative exposure of TSP from all five time periods. The TSP concentration at each time period was multiplied by the years between each time period and these values were summed across all five time periods to calculate cumulative exposure. Cumulative exposure was then categorized into quartiles based on the distribution of the controls and the lowest quartile was used as the referent. Only those participants with complete address data were used for the cumulative exposure analysis.

Results

We were able to successfully geocoded 79%, 87%, and 87% of the Erie and Niagara County birth, menarche, and first birth addresses, respectively. The descriptive characteristics of the participants included in the birth, menarche, first birth, and the overall case-control study are depicted in Table 1. There were no major differences between the distributions of these variables between each time period. The mean concentration of TSP at the first birth address compared with the birth and menarche addresses was considerably lower among premenopausal women for both cases and controls. To a much lesser extent, there was a reduction in mean TSP concentration at the first birth address among postmenopausal women. The ambient TSP concentrations at participants' addresses 20 and 10 years before interview were dramatically decreased prohibiting an analysis at these two time periods. The mean TSP concentrations 20 years before interview were 64 $\mu g/m^3$ (SD, 12.5 $\mu g/m^3$) and 63 $\mu g/m^3$ (SD, 11.8 $\mu g/m^3$) for premenopausal and postmenopausal women, respectively. The mean TSP concentration 10 years before interview was even lower and identical for premenopausal and postmenopausal women (44 $\mu g/m^3$; SD, 6.7 $\mu g/m^3$).

Exposure to concentrations of TSP >84 $\mu g/m^3$ at the time of birth was associated with an increase in the OR for premenopausal women (Table 2); however, there was no exposure-response relationship and the *P* for trend was not significant. In addition, there were relatively few participants

Table 1. Descriptive characteristics for study participants at birth, menarche, first birth, and overall study: Western New York exposures and breast cancer study (WEB study)

	Premenopausal Women							
	Birth		Menarche		First birth		Overall study	
	Cases (n = 164)	Controls (n = 283)	Cases (n = 204)	Controls (n = 386)	Cases (n = 181)	Controls (n = 371)	Cases (n = 325)	Controls (n = 610)
Age [y, mean (SD)]	44.3 (4.5)	43.8 (4.5)	44.5 (4.5)	43.8 (4.6)	44.5 (4.7)	44.2 (4.6)	44.9 (4.6)	44.1 (4.6)
Education [y, mean (SD)]	13.7 (2.6)	14.2 (2.2)	13.9 (2.0)	14.1 (2.2)	13.9 (2.0)	14.1 (2.1)	14.0 (2.3)	14.2 (2.2)
Age at menarche [y, mean (SD)]	12.5 (1.5)	12.6 (1.6)	12.5 (1.6)	12.6 (1.6)	12.5 (1.4)	12.7 (1.6)	12.5 (1.6)	12.6 (1.6)
Age at first birth [y, mean (SD)]	25.1 (4.8)	26.1 (4.5)	25.4 (4.9)	25.7 (4.8)	25.7 (7.2)	26.1 (4.9)	25.0 (5.1)	25.8 (4.8)
Body mass index [mean (SD)]	27.4 (7.2)	27.3 (6.3)	27.0 (6.9)	27.6 (6.8)	27.2 (7.2)	27.3 (6.6)	27.2 (6.8)	27.6 (6.7)
TSP [g/m^3,mean (SD)]	135.7 (27.1)	138.2 (33.4)	122.4 (34.4)	124.0 (37.2)	65.6 (32.0)	69.2 (36.7)	—	—
Benign breast disease (yes)	34%	22%	35%	20%	35%	22%	37%	21%
First-degree relative with breast cancer (yes)	23%	10%	23%	10%	21%	9%	21%	10%
	Postmenopausal women							
	Birth		Menarche		First birth		Overall study	
	Cases (n = 357)	Controls (n = 524)	Cases (n = 469)	Controls (n = 757)	Cases (n = 435)	Controls (n = 782)	Cases (n = 841)	Controls (n = 1,495)
Age [y, mean (SD)]	62.3 (7.9)	62.1 (9.1)	61.9 (8.1)	62.2 (9.1)	62.8 (8.3)	63.0 (8.9)	63.0 (8.5)	63.4 (8.9)
Education [y, mean (SD)]	13.4 (2.5)	13.0 (2.1)	13.4 (2.5)	13.0 (2.1)	13.2 (2.4)	13.0 (2.2)	13.3 (2.6)	13.0 (2.3)
Age at menarche [y, mean (SD)	12.4 (1.5)	12.8 (1.7)	12.5 (1.5)	12.8 (2.1)	12.6 (1.6)	12.8 (1.7)	12.6 (1.6)	12.8 (1.7)
Age at first birth [y, mean (SD)]	23.9 (4.5)	23.7 (3.9)	23.9 (4.5)	23.7 (6.3)	24.3 (4.8)	24.1 (4.4)	23.8 (4.7)	23.5 (4.3)
Body mass index [mean (SD)]	28.6 (5.9)	28.4 (6.1)	28.6 (5.8)	26.7 (6.3)	28.9 (5.8)	28.5 (5.9)	28.9 (6.0)	28.5 (6.1)
Age at menopause [y, mean (SD)]	48.3 (5.0)	47.4 (6.0)	48.0 (5.3)	47.6 (6.0)	45.9 (5.6)	47.6 (6.0)	48.3 (5.4)	47.4 (6.3)
TSP [g/m^3,mean (SD)]	141.4 (31.2)	137.7 (28.9)	139.1 (31.6)	138.1 (31.2)	126.7 (36.8)	127.9 (36.6)	—	—
Benign breast disease (yes)	36%	22%	34%	23%	34%	21%	33%	22%
First-degree relative with breast cancer (yes)	20%	14%	19%	15%	21%	13%	20%	14%

exposed to the lowest concentrations of TSP and this resulted in wide confidence intervals for the corresponding point estimates. In postmenopausal women, exposure to high concentrations of TSP (>140 g/m^3) was associated with an adjusted OR of 2.42 (95% CI, 0.97-6.09) compared with exposure to low concentrations (<84 g/m^3). For risk associated with estimated residential TSP concentrations on a continuous scale, in postmenopausal women, we observed a 20% increase in the odds ratio for every 30 μg/m^3 increase in TSP concentration (adjusted OR, 1.20; 95% CI, 1.04-1.38). In the spline regression analysis, there was an increase in the probability of being a case with an increase in TSP concentration (Fig. 2). No increase in risk was observed for premenopausal women on a continuous scale (OR, 0.92; 95% CI, 0.76-1.11 for every increase in 30 g/m^3 of TSP). Furthermore, the spline regression analysis for the premenopausal women indicated an inverted parabola exposure-response relationship with increasing TSP concentration (Fig. 3).

At menarche, exposure to high concentrations of TSP was also associated with a modest increase in the odds ratio for postmenopausal women with exposure >84 μg/m^3, although the P for trend was not significant (Table 3). In the continuous analysis, for every 30 g/m^3 increase in TSP concentrations at menarche, the odds ratio increased 8% (adjusted OR, 1.08; 95% CI, 0.96-1.21) for postmenopausal women. The risk estimates for the premenopausal women were not consistent with our hypothesis. In this group, there was a nonsignificant reduction in risk in the highest exposure category (adjusted OR, 0.66; 95% CI, 0.38-1.16). Exposure to high concentrations of TSP at the time of first birth was also associated with a modest increase in the OR for postmenopausal women (Table 4). For premenopausal women exposed to high concentration of TSP, there was some indication of a nonsignificant reduction in the OR (OR, 0.52; 95% CI, 0.22-1.20).

Lifetime cumulative exposure to TSP was associated with an increase among postmenopausal breast cancer only (2nd quartile OR, 3.2; 95% CI, 1.5-7.3; 3rd quartile OR, 4.2; 95% CI, 1.8-9.7; 4th quartile OR, 3.5; 95% CI, 1.4-8.9); the test for trend was 0.03. When the second, third, and fourth quartiles were combined, the adjusted OR for the upper category was 3.6 (95% CI, 1.6-7.9). For premenopausal women, cumulative exposure was not associated with the risk of breast cancer (2nd quartile OR, 0.7; 95% CI, 0.4-1.2; 3rd quartile OR, 0.5; 95% CI, 0.3-1.7; 4th quartile OR, undefined), although few premenopausal women had cumulative exposure in the 3rd or 4th quartiles.

Discussion

Whereas numerous epidemiologic studies have investigated the carcinogenicity of air pollution in relation to lung cancer, (25-27) to our knowledge, no investigations have examined exposure to TSPs and breast cancer. The findings from this

Table 2. Risk associated with exposure to TSP concentrations at birth address: Western New York exposures and breast cancer study (WEB study)

TSP ($\mu g/m^3$)	Premenopausal				Postmenopausal			
	Cases (n = 164)	Controls (n = 283)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Cases (n = 357)	Controls (n = 521)	Crude OR (95% CI)	Adjusted OR (95% CI)*
<84	5	16	1.00	1.00	7	19	1.00	1.00
84-114	26	46	1.81 (0.59-5.51)	1.96 (0.64-3.01)	52	67	2.11 (0.82-5.39)	2.32 (0.89-6.10)
115-140	64	92	2.23 (0.78-6.39)	2.23 (0.77-6.44)	142	223	1.73 (0.71-4.21)	1.94 (0.77-4.86)
>140	69	129	1.71 (0.60-4.87)	1.78 (0.62-5.10)	156	215	1.97 (0.81-4.80)	2.42 (0.97-6.09)
P for trend				0.38				0.01

*Adjusted for age, education, and parity.

study suggest that early life exposure to high concentrations of TSP, a proxy measure of PAHs, may be associated with an increased risk of breast cancer in postmenopausal women. We found >2-fold increase in risk for those with a birth residence in areas where exposure was >140 $\mu g/m^3$ compared with those with a birth residence where concentration was less than 84 $\mu g/m^3$. Exposure at menarche and first birth were less strongly associated with risk, although we were unable to examine the independent effect of each time period because they were highly correlated. Furthermore, cumulative exposure to TSP was associated with postmenopausal breast cancer. The cumulative exposure score, however, was largely a function of exposure at birth and menarche.

There was little evidence that early life exposure to high concentrations of TSP was positively associated with premenopausal breast cancer, although not significant, the OR for the birth analyses was slightly elevated. However, the inconsistency of these findings at menarche and first birth for women in this group may be attributed to insufficient induction time between exposure in early life and the occurrence of breast cancer. Another possible explanation is that cumulative exposure was lower for premenopausal women than for postmenopausal women. For instance, whereas premenopausal and postmenopausal women had similar TSP concentrations at birth, TSP concentrations dramatically declined for premenopausal but not postmenopausal women between the time of menarche (median year, 1966) and first birth (median year, 1977). Correspondingly, few premenopausal women, cases or controls, were in the upper quartiles of cumulative exposure and there was no evidence of an association between cumulative exposure and premenopausal breast cancer.

Several previous studies have examined exposure to PAHs in adult life in relation to cancer (10, 11). There is evidence that PAH-DNA adducts in tumor tissue and peripheral blood tends to be higher in breast cancer cases that in controls. Tumor PAH-DNA adducts levels are markers of recent exposure and PAH-DNA adducts in mononuclear cells are at best indicative of exposure several years before collection. Our findings are based on historical estimates of early life exposure. They support the hypothesis that exposure to PAHs may be associated with breast cancer risk and indicate that early life exposure to these compounds may have particular relevance to the etiology of breast cancer.

Other exposures, particularly ionizing radiation, have been observed to increase risk of breast cancer with early age at exposure. Similarly, exposure to PAHs in early life may also confer increased risk of breast cancer compared with adult exposure to PAHs. In addition, there is some evidence that early life exposure to PAHs could affect the developing fetus. In a study of early life exposure to high PAHs concentrations in air, Perera et al. found exposure to PAHs was associated with reduced birth weight, birth length, and head circumference (28). Several studies investigating the relationship between birth weight and the risk of breast cancer have observed a j-shaped curve with birth weight; those <2,500 g at birth had increased risk of breast cancer

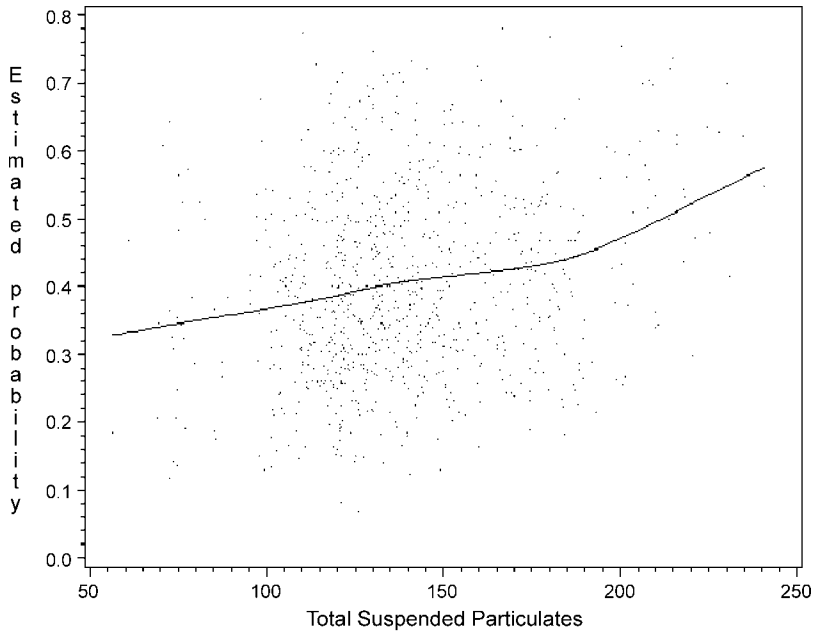

Figure 2. Estimated probability of being a case for postmenopausal women by TSP concentration ($\mu g/m^3$) at birth address.

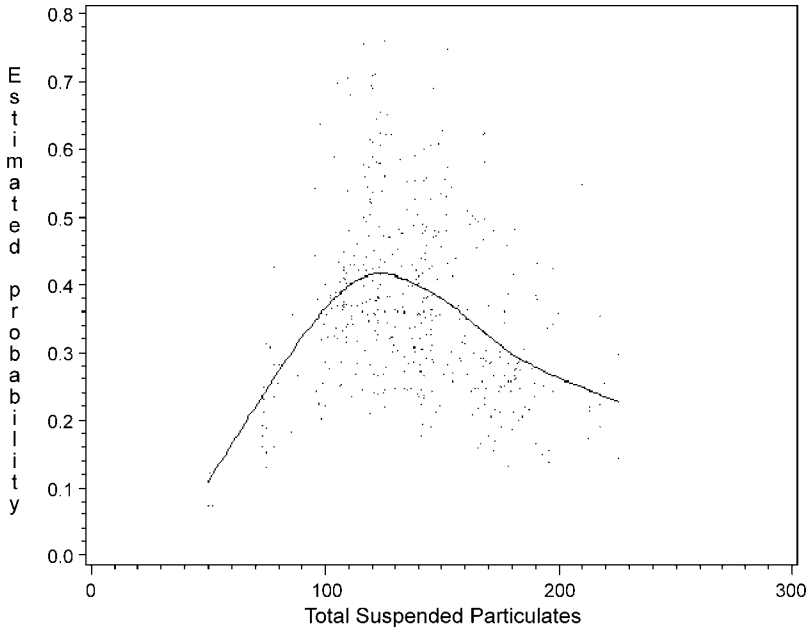

Figure 3. Estimated probability of being a case for premenopausal women by TSP concentration ($\mu g/m^3$) at birth address.

compared with women with birth weights of 2,500 to 2,999 g (29, 30).

It is also possible that PAHs may not affect breast cancer risk and our findings are a result of other carcinogens and cocarcinogens found in TSPs. We speculated that PAHs physically associated with TSP may be the agent responsible for the association between TSP and breast cancer risk that we observed. However, we cannot rule out the possibility that other compounds present in TSP are affecting breast cancer risk or are acting synergistically with PAHs. In experimental studies, for instance, application of coal tar produced more skin tumors than did the application of only benzo(a)pyrene, which is thought to be the primary carcinogen in coal tar. Other constituents in coal tar seem to contribute to the carcinogenic potential and enhance synergistically the effect of benzo(a)pyrene (9). It may be that it is the mixture of compounds in TSP that is relevant to breast cancer risk.

Several methodologic concerns need to be considered when interpreting our findings. Foremost is the potential for selection bias to affect the internal validity of the study. To investigate the extent of the geographic selection bias, we compared the geographic distribution of breast cancer cases in the study with that of the breast cancer cases reported to the New York State Tumor Registry. The expected number of cases per zip code in Erie and Niagara Counties were obtained from the NY State Tumor Registry and compared with the number of cases identified for our study. Overall, there was some evidence that cases identified for this study tended to reside more closely to the study site than cases identified in the NY State Tumor Registry. When the expected number of controls per zip code (obtained from the 1990 U.S. Census) was compared with the number of controls observed in our study, controls in our study were also more likely to currently reside more closely to the study site.

In addition, there is the possibility that our results were biased because the sample was restricted to women who were both current residents of Erie or Niagara Counties at the time of the case-control study and who had lived there during their earlier life. However, we found little difference between those subjects with birth addresses in Erie and Niagara Counties compared with those subjects with birth addresses outside of these two counties with regard to demographic characteristics or established risk factors (data not shown).

Small numbers in some categories and the resultant large confidence intervals affected our ability to draw conclusions from our data. The distribution of TSP concentrations contributed to the small numbers in certain categories. Ambient TSP concentrations had large spatial variation in the 1960s, but in general, TSP concentrations were high compared with later time periods. However, TSP concentrations began to decrease in the early 1970s leading to low estimates in the 1970s to 1990s with very little geographic variation in TSP concentrations. Consequently, the distributions for each time period were very different. Few postmenopausal participants were exposed to low

Table 3. Risk associated with exposure to TSP concentrations at menarche address: Western New York exposures and breast cancer study (WEB Study)

TSP ($\mu g/m^3$)	Premenopausal				Postmenopausal			
	Cases (n = 204)	Controls (n = 386)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Cases (n = 469)	Controls (n = 757)	Crude OR (95% CI)	Adjusted OR (95% CI)*
<84	32	66	1.00	1.00	14	28	1.00	1.00
84-114	53	99	1.10 (0.65-1.89)	0.98 (0.56-1.70)	81	120	1.35 (0.67-2.72)	1.36 (0.67-2.77)
115-140	62	81	1.58 (0.92-2.70)	1.25 (0.71-2.23)	171	298	1.15 (0.59-2.24)	1.20 (0.61-2.36)
>140	57	140	0.84 (0.50-1.42)	0.66 (0.38-1.16)	203	311	1.31 (0.67-2.54)	1.45 (0.74-2.87)
P for trend				0.21				0.18

*Adjusted for age, education, and parity.

Table 4. Risk associated with exposure to TSP concentrations at first birth address: Western New York exposures and breast cancer study (WEB study)

TSP ($\mu g/m^3$)	Premenopausal				Postmenopausal			
	Cases (n = 181)	Controls (n = 371)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Cases (n = 435)	Controls (n = 782)	Crude OR (95% CI)	Adjusted OR (95% CI)*
<84	147	294	1.00	1.00	54	102	1.00	1.00
84-114	19	30	1.27 (0.69-2.33)	1.06 (0.55-2.02)	89	150	1.12 (0.74-1.71)	1.30 (0.83-2.03)
115-140	5	19	0.53 (0.19-1.44)	0.41 (0.14-1.67)	142	260	1.03 (0.70-1.52)	1.28 (0.83-1.97)
>140	10	28	0.71 (0.34-1.51)	0.52 (0.22-1.20)	150	270	1.05 (0.71-1.24)	1.33 (0.87-2.06)
P for trend				0.04				0.61

*Adjusted for age, education, and parity.

concentrations at birth and few premenopausal women were exposed to high concentrations at the time of first birth. These trends in ambient air concentration of TSP precluded an analysis of exposure in adult life up to the time of diagnosis because the lack of variability. To be able to make comparisons between time periods, we chose to use a common cut point for all analyses. The cut points for our analyses were arbitrarily selected based on the distribution of the TSP measurements in the 1960s. With the majority of participants having had high levels of TSP at birth, these cut points resulted in small numbers in the referent group. However, the continuous and spline regression analyses support the direction of the association in postmenopausal women.

In addition to the secular changes in ambient TSP concentrations, TSP is a relatively crude measure of ambient air pollution. In 1987, it was replaced with particulate matter <10 μm (31). Currently, particulate matter <2.5 μm is considered to be the most relevant measure for biological effects of air pollution because these fine particles are respired into the lower respiratory tract (5). However, TSP concentrations were the only consistently measured ambient air pollutant in the early 1960s, the period before the Clean Air Act, which led to reductions in ambient air pollution. TSP is the best available measure to estimate historical exposure to air pollution. Nevertheless, there remains the potential for exposure misclassification because TSP concentration measurements were used as a surrogate for exposure to PAHs. PAHs exist in the ambient air in both the gaseous and particulate phase. The use of TSP captures exposure to PAHs in the particulate phase only (32), although ambient benzo(a)pyrene concentrations were highly correlated (r = 0.90) with TSP concentrations in this region. In addition, the interpolation method used to estimate concentrations of TSP at residential addresses likely contributed some error. The air samplers were not randomly distributed throughout Erie and Niagara Counties. In general, air samplers were placed in regions thought to have high levels of air pollution. Because the monitoring system was not designed to provide county wide characterization of TSP levels, some outlying areas were never monitored and were approximately 18 miles from the closest monitor.

Another potential problem in assessing exposure arose because humans are peripatetic (33). Therefore, our estimates of TSP concentrations are site specific for each participant and may not represent exposures at other places where these participants spent time. This is likely less of a problem for the analyses of birth residence. By menarche, however, these participants may spend a considerable proportion of their time away from home. Similarly, exposure misclassification may have arisen because we lacked information on TSP exposure that occurred outside of the study area, although the misclassification is likely to be nondifferential between cases and controls.

In summary, we examined exposure to TSPs, a surrogate for PAHs exposure, in relation to the risk of breast cancer. We found a suggestion of an association between exposure to high concentration of TSP at birth and an increase risk of breast cancer in postmenopausal women. Among premenopausal women, there was no evidence of such an association with risk of breast cancer. Whereas, these results are suggestive, they necessarily should be considered preliminary. Future research on the effects of early life exposure to PAHs and other related compounds is warranted.

Acknowledgments

We thank Dr. Takuma Nemoto and Dominica Vito for their contributions to this study.

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Cancer Epidemiol Biomarkers Prev 2005;14:53-60.