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Women's occupational exposure to polycyclic aromatic hydrocarbons and risk of breast cancer

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Abstract

Objective: To estimate the association between occupational polycyclic aromatic hydrocarbon (PAH) exposure and breast cancer.

Methods: Lifetime work histories for 1,130 cases and 1,169 controls from British Columbia and Ontario (Canada) were assessed for PAH exposure using a job-exposure matrix based on compliance measurements obtained during U.S. Occupational Safety and Health Administration workplace safety inspections.

Results—We observed increased risk of breast cancer for women who were ever-exposed to PAHs (OR = 1.32, 95% CI: 1.10–1.59), and an increased risk with duration at "high" PAH exposure (for >7.4 years: OR = 1.45, 95% CI: 1.10–1.91; p_{trend} = 0.01). Risk of breast cancer from prolonged occupational PAH exposure was stronger among premenopausal women (for >7.4

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years: OR = 1.74, 95% CI: 1.10–2.74; p_{trend} = 0.01) and women with a family history of breast cancer (for >7.4 years: OR = 2.79, 95% CI: 1.25–6.24; p_{trend} < 0.01).

Conclusions: Our study suggests that prolonged occupational exposure to PAH may increase breast cancer risk, especially among women who are either premenopausal, or have a family history of breast cancer.

Keywords

breast cancer; workplace exposure; occupational exposure; PAH; case-control study; job-exposure matrix

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) are a large group of chemical compounds formed as by-products of combustion involving organic matter and are common environmental pollutants. Exposure to PAHs occurs through several sources including diet, air pollution, and smoking.[1] Low-level environmental PAH exposure is ubiquitous, but differences in PAH exposure can be influenced by more intense occupational exposures.[1 2] Experimental studies show that metabolic activation of PAH to carcinogenic metabolites, including diol-epoxides and quinones,[3–5] is mediated by enzymes that exist in all tissues.[5–8] Mammary tissues bioaccumulate PAHs,[9] thereby creating a potential concentration of PAH-derived carcinogens that may contribute to increased risk of breast cancer.

The association of PAH exposure and risk of female breast cancer remains unclear. Two recent Danish studies examined air pollution exposure and breast cancer risk: one, which involved examining a complex mixture of PAH and non-PAH exposure, found no association with breast cancer,[10] while the other found a positive association.[11] However, the majority of studies to date focused on ambient air pollution, smoking, and other sources that confer exposure that is, compared to PAH-contaminated workplaces,[12–17] much lower in intensity. Three studies that investigated the association of occupational PAH exposure and breast cancer observed an increased risk.[18–20]

Our objective was to evaluate the association between breast cancer among women employed in industries with PAH exposure, and to assess potential interactions with menopausal status, tumour pathology, family history, and other biological and socioeconomic factors.

METHODS

Study Population

A population-based case-control study of female breast cancer was conducted in the greater metropolitan area of Vancouver, British Columbia (BC) and Kingston, Ontario, between 2005 and 2010. Results for shift work,[21] physical activity,[22] and genetic variants[23–25] have been published. Ethics approval was provided by the University of British Columbia / BC Cancer Agency Research Ethics Board and the Queen's University Health Sciences

Research Ethics Board. Prospective participants were mailed a study package that included a consent form and questionnaire.

Greater Vancouver—Breast cancer cases were recruited from the BC Cancer Registry. Cases were women between 40–80 years of age, diagnosed with either *in situ* or invasive breast cancer, no previous cancer history except for non-melanoma skin cancer, and were living in the cities of Vancouver, New Westminster, Richmond, or Burnaby at the time of diagnoses. Controls were women recruited from the Screening Mammography Program of BC who consented to participate during routine screening mammography and were living in the same geographic areas. Controls were frequency-matched to cases by age in 5-year groups. Response rate among cases and controls were 54% (n = 1,001) and 57% (n = 1,014), respectively.

Kingston—Cases and controls were recruited from the Hotel Dieu Breast Assessment Program in Kingston, Ontario. Eligible participants were women under the age of 80 years with no previous cancer history except non-melanoma skin cancer, and not currently receiving cancer preventive drugs. Cases had a subsequent diagnosis of either *in situ* or invasive breast cancer, and controls had either normal mammography results or a diagnosis of benign breast disease. Controls were frequency-matched to cases by age in 5-year groups. Response rate among cases and controls were 59% (n = 131) and 49% (n = 164), respectively.

Due to minimum age restrictions for screening mammography in BC, Ontario participants under 40 years of age were excluded, reducing the number of eligible participants to 129 cases and 155 controls. Overall, a total of 1,130 cases and 1,169 controls were included in the analysis. Participants signed a consent form and completed a questionnaire, including questions relating to demographics, medical and reproductive history, and lifestyle factors, and was either self-administered and mailed (n = 726 cases, n = 825 controls) or administered by telephone interviews in English, Cantonese, Mandarin, or Punjabi (n = 404 cases, n = 344 controls).

Lifetime work history, which included start and end dates, industry, occupation, and tasks performed for any job held for at least six months, was used to infer PAH exposure using a job exposure matrix (JEM) based on a statistical model[26] of coal tar pitch volatiles (CTPV), a common PAH surrogate. Industries were classified using the North American Industry Classification System (NAICS) 2007 (Canadian edition) and occupations were classified using the Standard Occupation Classification (SOC) 2010 (US edition). Industrial classification was done manually, while occupational classification was automated[27] and then manually reviewed to ensure accuracy. The JEM estimates the probability of job-specific exposure (τ) exceeding the permissible exposure level (PEL = 0.2 mg·m^{-3}) for PAHs ($\theta = Pr(\tau > PEL)$). Jobs with “high” exposure were defined as those with at least 9% probability of exceeding PEL; this corresponded to the 50th percentile of non-zero probabilities assigned to all occupations among controls. Intermediate exposure groups were defined as “low” (θ = 0.1–2.9%) and “medium” (θ = 3.0–8.9%), which corresponded to less than the 25th and between the 25th and 50th percentile, respectively, and jobs with zero probability of exceedance were treated as unexposed. The number of years employed in

each occupation was calculated accounting for part-time work via adjustment to full-time equivalent duration based on a 40-hour work week. Duration of exposure was calculated for each level and categorized based on the tertiles among the controls.

A second exposure metric, weighted duration of exposure, is defined in equation (1):

$$\text{Weighted Duration}_i = \sum_{k=1}^{K_i} \left(\text{PP}_{i,k} \times \text{D}_{i,k}\right) \quad (1)$$

where $\text{PP}_{i,k}$ is the predicted probability from the JEM for participant i during job number k, $\text{D}_{i,k}$ is the duration, and K_i is the total number of jobs reported by participant i in the study. Weighted duration is analogous to cumulative exposure but uses probability instead of intensity.

A third exposure metric utilized is the average probability of exposure weighted by duration defined by equation (2):

$$\text{Average Probability}_i = \frac{\sum_{k=1}^{K_i} \left(\text{PP}_{i,k} \times \text{D}_{i,k}\right)}{\sum_{k=1}^{K_i} \text{D}_{i,k}} \quad (2)$$

Exposure assessments were modified based on the participants' reported tasks and materials handled. For example, if the JEM assigned no exposure, but the participant indicated they worked with materials known to be a source for PAHs, the exposure level for that job was modified based on *a priori* criteria (APPENDIX).

Statistical Analysis

Multivariable logistic regression was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CI) to examine the relationship between occupational PAH exposure and breast cancer risk. To ensure that the referent group was truly unexposed when examining duration of medium and/or high exposure, a nuisance variable: {1 if maximum exposure level was low, 0 elsewhere} and {1 if maximum exposure level was low or medium, 0 elsewhere} was used to adjust for low and/or medium exposure, respectively. *A priori* confounders age (continuous), centre (Kingston vs. Vancouver), and education were included in all models, and additional potential confounders were selected using an all-possible-model backwards selection procedure.[28] Retention of a confounder occurred if it altered the OR for the "highest probability" or "longest duration" exposure levels by 10% or more. Potential confounders included ethnicity, self-reported body mass index (BMI), medical history (e.g. use of oral contraceptives), menopausal status as defined by guidelines similar to Friedenreich *et al.*,[29] age of menarche, parity, age at first birth, age at first mammogram, first-degree family history of breast cancer, and smoking status and pack-years of cigarettes.

To test for trends in exposure variables, exposure levels were treated as continuous variables (i.e. none = 0, low = 1, medium = 2, and high = 3). Interactions with menopausal status, smoking (pack-years), and ethnicity were assessed through stratified analysis and interaction

terms in the logistic models. Ethnicity was stratified as European vs. Asian (Chinese, Japanese, or Korean); all other ethnicities were excluded due to insufficient sample sizes. Supplemental analyses were conducted to estimate interactions with socioeconomic status (SES), BMI, and first-degree family history of breast cancer; first degree was defined as having at least one immediate family member (e.g. mother, sister, or daughter) diagnosed with breast cancer. A case-only logistic model was used to evaluate whether PAH exposure-related breast cancer risk differed between hormone receptor positive (ER/PR: +/−, −/+, or +/+) and negative (−/−) cases. The impact of using different sources for cases and controls in Vancouver was assessed by excluding cases not registered in the screening mammography program (n = 227). All analyses were conducted using the statistical software R (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cases were more likely to have ever been pregnant, older at first pregnancy, had fewer subsequent pregnancies, and did not breastfeed as long as controls (Table 1). Although cases were more likely to have ever been pregnant, the effects were null after adjustment for confounders. Cases tended to be older at time of first mammogram, more likely to have had a (first-degree) family history of breast cancer, and smoked more. Compared to cases, controls were more likely to be of European descent, have a higher SES (i.e. family income greater than $80,000, and/or received a graduate/professional school degree), have used oral contraceptives, and were less likely to be overweight or obese.

Table 2 shows adjusted ORs from the logistic models for the various exposure metrics. Approximately 64% of participants were ever employed in an occupation with a non-zero probability of PAH exposure above the PEL ($\theta > 0\%$), with about 40% ever employed in at least one occupation that was classified as a “high” risk of receiving PAH exposure ($\theta \geq 9\%$). This is not surprising, as PAHs are by-products of combustion and the most common industry participants were employed in that was at risk for exposure was the food-service industry (Supplementary Table A1).

Exposure to “any” level of PAHs was associated with an increased breast cancer risk (OR = 1.32, 95% CI: 1.10–1.59). Elevated risk was also apparent for having ever been employed in a job with “high” exposure (OR = 1.43, 95% CI: 1.17–1.76). Dose-response was evaluated through duration at any level, at medium and/or high, and at high levels of PAH exposure; elevated risk was observed for each duration level of exposure. Evidence of increased risk with duration was apparent for “medium or high” exposure levels (the longest duration: OR = 1.41, 95% CI: 1.10–1.81) and “high” exposure levels (the longest duration: OR = 1.45, 95% CI: 1.10–1.91). Similarly, weighted duration (Eq. 1) and average probability (Eq. 2) both provided evidence of an exposure-response ($p_{trend} < 0.01$), with women in the longest duration category and the highest tertiles exhibiting increased risk for breast cancer. Analyses involving only the *a priori* confounders (age, centre, and education) yielded similar results, although the ORs were slightly inflated compared to the analysis with the final set of confounders.

No differences in the overall PAH-breast cancer associations were observed by menopausal status (Table 3). However, among premenopausal women, a dose-response trend was observed with prolonged duration at both “medium or high” and “high” exposure (medium-high: OR = 1.68, 95% CI: 1.12–2.52; high: OR = 1.74, 95% CI: 1.10–2.74; all $p_{trend} = 0.01$). Similarly, for weighted duration and average probability, the highest and the longest tertiles showed increased breast cancer risk (average probability: OR = 1.50, 95% CI: 1.04–2.17, $p_{trend} = 0.02$; weighted duration: OR = 1.58, 95% CI: 1.08–2.29, $p_{trend} < 0.01$) among premenopausal women.

A total of 844 cases were classified as hormone receptor positive and 166 as hormone receptor negative. No differences in breast cancer risk were observed by receptor status (interaction p-values > 0.5); however, some associations with exposure were attenuated among ER/PR− cases (Supplementary Table A2). Sensitivity analysis, which excluded cases not enrolled in the screening clinic that controls were recruited from, yielded similar results as the full cohort. Similarly, no differences were observed when stratifying by smoking status, ethnicity, SES or BMI (not shown). Family history was associated with an increased risk of breast cancer (Table 4), especially among those with the longest duration at high exposure (OR = 2.79, 95% CI: 1.25–6.24), the longest weighted duration (OR = 2.26, 95% CI: 1.19–4.28), and those exposed at the highest level of average probability (upper tertile: OR = 2.55, 95% CI: 1.34–4.84); all exposure metrics displayed positive dose-response trends (all $p_{trend} < 0.01$). Given that the majority of participants were from BC, a sensitivity analyses involving the BC-only cohort were performed; there were no important differences compared to the full cohort (not shown).

DISCUSSION

The results provide evidence of increased risk of breast cancer associated with estimated occupational exposure to PAHs. The effect appeared stronger among premenopausal women, but data do not support a measurable heterogeneity of effect. The estimated effect of PAH on breast cancer risk was stronger among women with a first-degree relative with breast cancer. Differences in risk were not apparent by either hormone receptor status,, ethnicity, SES, BMI, or smoking.

Similar to our results, Petralia *et al.*[18] observed elevated risks among premenopausal women with medium-to-high (average) probability of PAH exposure (OR = 2.40, 95% CI: 0.91–6.01). Petralia *et al.* reported no evidence of association with either cumulative exposure (analogous to our weighted duration), or duration of exposure; however, their results are not directly comparable to ours. Probabilities expressed by Petralia *et al.* were ordinal categories representing the likelihood of PAH exposure, whereas we expressed probabilities as continuous estimates that reflect the likelihood of *excess* PAH exposure, i.e. above the PEL. Nonetheless, our results support their observed association between occupational PAH exposure and breast cancer risk.

On average, first-degree family history of breast cancer is a known to double the risk of breast cancer.[30] Estimated effects PAH exposure on breast cancer risk were stronger in women with first-degree family history, doubling on average in the highest exposure groups.

Given the role genetics play in the etiology of breast cancer, the heterogeneous effects support the notion of interactions between PAH exposure and genetic susceptibility. In particular, certain enzymes metabolize xenobiotic agents into procarcinogens[6 8] and there is evidence of interactions between PAH-DNA adduct levels and metabolism-related genes[31 32] that can elevate breast cancer risk.[14] Moreover, a recent study by Shen *et al.* observed an increased risk of breast cancer associated with PAH-DNA adducts and evidence that supports a gene-environment interaction between PAH exposure and family-history.[33]

The hypothesized interaction between exposure and tumour estrogen receptor status is based on the observation that PAHs trigger estrogenic and antiestrogenic responses,[34] which can increase the formation of quinones.[5] The slightly stronger associations observed between PAH exposure and breast cancer risk among ER/PR+ cases are consistent with this idea; however, our results are equally likely due to chance. However, the manner in which prolonged PAH exposure modifies estradiol metabolism could help explain the risk differences observed among pre and postmenopausal women. Due to their lipophilic nature,[1 2] the effects of PAH exposure were thought to stronger among those with higher BMI; however, we observed no indication of a difference in risk by BMI. Different sources for recruitment of participants in Vancouver did not alter our results, suggesting negligible selection bias. However, the relatively low participation rate among both cases and controls could lead to selection bias that may impact the results in ways that are impossible to discern.

Implementing a JEM derived from workplace measurements is a major strength of our study. Although others used “industry” to assess PAH exposure,[35 36] JEMs identify risks associated with specific occupations are better at capturing inter-personal variation in exposure.[37] A concern with expert-based JEMs is that they are based solely on expert opinion that are assured to be imperfect, leading to misclassification. For example, the food-service industry, which employed more than 20% of participants during their respective careers, is at high risk of PAH exposure based on the OSHA data.[26] The measurement-based JEM estimated the likelihood of exposure above PEL to be between 44–88% depending on occupation, while two expert-based JEMs, which were obtained for comparative purposes, classified the majority occupations in the food-service industry as low risk of exposure or no exposure. Moreover, as opposed to ordinal rankings of previous or older exposure metrics, measurement-based JEMs provide quantifiable estimates that are less arbitrary, more easily interpretable, and are based on empirical evidence rather than potentially biased opinions. Given the population of interest, where the majority of the industries studied (e.g. aluminum smelting) were male-dominated, using older JEMs can pose issues as the expert judgement was based mostly on male samples. Additionally, a measurement-based JEM can be updated over time as more data becomes available. This flexibility is particularly important because the analytical methodology for determining CTPV levels (e.g. HPLC) has changed during the thirty-year span of the database and therefore exceedance risk could be time-dependent; previous analyses of the OSHA data for PAHs found no temporal effects.[26] However, the measurements have some limitations, including using CTPV as a surrogate for PAHs. Sources for PAHs are a complex mixture, both chemically and toxicologically, and therefore identifying the exact PAH or the toxicological effect is difficult, especially given their varying toxic equivalency (e.g. benzo[α]pyrene is more toxic than chrysene).

Subsequently, this measurement-based JEM is estimating a surrogate (e.g. job in place of actual measurement) of a surrogate (e.g. CTPV in place of PAHs), and therefore misclassification would occur if the ratio of total PAHs to CTPV differs substantially among occupations. The use of non-random measurements is another potential limitation, as the choice of when (i.e. programmed or surprise inspections) to measure may bias the results; OSHA inspections are determined by responses to employee complaints, community concerns, and reports of incidents. However, analyses of one of the two OSHA databanks found that detected concentrations for 219,000 measurements were similar for surprise and programmed inspections.[38] The anchoring of our JEM in measurements and the probability of exceeding workplace exposure limits is among the strengths of the innovative approach to exposure assessment that we adopted.

Differential misclassification is a potential limitation of using JEMs for classifying exposure status, and can arise from dichotomizing imperfectly assessed exposure when true exposure and the outcome are related, even in cases where the error in exposure is non-differential with respect to the outcome.[39] Furthermore, all JEMs assign exposure at the group level that involves a mixture of truly exposed and unexposed individuals that can produce complex biases.[40] However, given the varying thresholds and indices used to define “exposed”, there is some assurance that the association between occupational PAH exposure and breast cancer, or at least within premenopausal women or those with a family history, is not due to chance. Lastly, although participants reported lifetime work history retrospectively, it is highly unlikely that recall bias plays a role in this analysis since women were unaware of the specific exposure of interest.

Tobacco smoke is a known source of PAH exposure, with some studies suggesting that long duration of smoking can result in an increased risk of breast cancer among women.[16 17] In our study, similar risks with PAH exposure were observed with smoking, and there was no evidence of interactions. However, it may not be appropriate to directly compare risks from occupational and non-occupational PAH sources (e.g. smoking and diet). Different PAH sources result in complex mixtures of PAHs and other compounds that can alter the toxicity of the mixture as a whole. As such, identifying risk posed by individual PAHs is near impossible in epidemiological research. Although we were unable to identify differences in effect by smoking, there was an increase in risk among smokers with the longest weighted duration of PAH exposure (OR = 1.50, 95% CI: 1.04–2.18; p_{trend} = 0.04).

In summary, PAH exposure was assessed through a novel measurement-based JEM and related to risk of breast cancer risk among over 2,000 women. Results support the notion that prolonged occupational exposure to PAHs in jobs with a measurable chance of exceeding occupational exposure limit is associated with increased breast cancer risk, especially among premenopausal women and those with a first-degree family history of breast cancer. Furthermore, the observation of an effect modification by family history supports the notion that a genetic factor plays a role in PAH exposure-related breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

- Polycyclic aromatic hydrocarbons (PAHs) are a group of environmental pollutants, many of which are considered carcinogenic, and are associated with multiple cancer sites.
- Although PAH exposure can play a role in development of female breast cancer, few studies have explored the risk from occupational exposures to PAHs.

What are the new findings?

- This study found that women exposed to occupational PAH had a higher risk of developing breast cancer, and that the risk was related to the probability and duration of exposure.
- These results provide additional evidence for women to be protected from exposure to PAH in the workplace.

How might this impact on policy or clinical practice in the foreseeable future?

- Given the implications of the study relate to workplace safety, the findings may affect safety standards, practices, and policies, or at the very least, make the public more aware of the consequences of prolonged employment in industries with this potential exposure

Table 1:

Descriptive Statistics of the Study Population

Variable	Cases (%)	Controls (%)	
Age			
Mean, Standard deviation (SD)	56.82, SD=10.29	56.39, SD=9.90	
Education			
High School or less	389 (34.5)	300 (25.7)	
College/Trade certificate	339 (30.0)	347 (29.7)	
University degree	271 (24.0)	299 (25.6)	
Graduate or professional school degree	130 (11.5)	223 (19.1)	
Household income			
Less than $15,000	70 (6.2)	32 (2.7)	
$15,000 to $29,999	140 (12.4)	89 (7.6)	
$30,000 to $59,999	281 (24.9)	268 (22.9)	
$60,000 to $79,999	139 (12.3)	158 (13.5)	
$80,000 or more	350 (31.0)	463 (39.6)	$p_{trend} < 0.01$
Not stated	150 (13.3)	159 (13.6)	
Ethnicity [a]			
European	703 (62.2)	912 (78.0)	
Chinese	239 (21.2)	115 (9.8)	
South Asian	32 (2.8)	34 (2.9)	
Filipino	60 (5.3)	38 (3.3)	
Japanese	24 (2.1)	14 (1.2)	
Other	50 (4.4)	42 (3.6)	
Mixed	22 (1.9)	14 (1.2)	$p < 0.01$
BMI			
Mean, SD	25.61, SD=5.27	25.15, SD=5.00	$p = 0.05$
Underweight (< 18.5)	27 (2.4)	27 (2.3)	
Normal (18.5 – 25)	585 (52.1)	665 (57.3)	
Overweight (25 – 30)	336 (29.9)	309 (26.6)	
Obese (30+)	174 (15.5)	159 (13.7)	$p_{trend} = 0.03$
Reproductive History			
Menopausal status			
Premenopausal	434 (38.4)	474 (40.5)	
Postmenopausal	695 (61.6)	695 (59.5)	$p = 0.30$
Ever Pregnant			
Never	191 (16.9)	240 (20.5)	
Ever	937 (83.1)	928 (79.5)	$p = 0.03$
Lifestyle			
Age at first mammogram			
Years: Mean, SD	44.69, SD=8.99	42.72, SD=7.70	$p < 0.01$
Family History of Breast Cancer			

Variable	Cases (%)	Controls (%)	
Never	906 (80.2)	1002 (85.7)	
Ever	224 (19.8)	167 (14.3)	p < 0.01
Smoking			
Current Smoker			
No	1057 (93.7)	1096 (93.8)	
Yes	71 (6.3)	72 (6.2)	p = 0.90
Pack-years			
Years: Mean, SD	5.63, SD=11.97	5.33, SD=11.33	p = 0.72

Table 2:

PAH exposure and breast cancer risk based on variations of the job exposure matrices[≠]

Exposure Assessment	Cases (%)	Controls (%)	OR	95% CI	
Ever-Never: Any level					
Never	342 (31.3)	454 (39.8)	-----		
Ever	749 (68.7)	687 (60.2)	**1.32**	**1.10**	**1.59**
Ever-Never: At maximum level[†]					
Never	342 (31.3)	454 (39.8)	-----		
Maximum level at low[*]	90 (08.2)	107 (09.4)	1.02	0.74	1.42
Maximum level at medium[¶]	175 (16.1)	178 (15.6)	1.26	0.97	1.64
Maximum level at high[◆]	484 (44.4)	402 (35.2)	**1.43**	**1.17**	**1.76**
				$p_{trend} < 0.01$	
Duration (years) of exposure at any level					
None (0)	342 (31.3)	454 (39.8)	-----		
Short (0.1–4.2)	235 (21.5)	229 (20.1)	**1.42**	**1.12**	**1.80**
Moderate (4.3–13.0)	256 (23.6)	230 (20.1)	**1.34**	**1.06**	**1.71**
Long (13.1–82.2)	258 (23.6)	228 (20.0)	1.20	0.94	1.53
				$p_{trend} = 0.09$	
Duration (years) of exposure at medium[¶] or high[◆] levels					
None (0)	342 (31.3)	454 (39.8)	-----		
Ever: Maximum at low level[Δ]	90 (08.2)	107 (09.4)	1.02	0.74	1.41
Short (0.1–2.7)	203 (18.6)	194 (17.0)	**1.41**	**1.10**	**1.81**
Moderate (2.8–9.0)	203 (18.6)	196 (17.2)	**1.32**	**1.02**	**1.70**
Long (9.1–80.8)	253 (23.2)	190 (16.7)	**1.41**	**1.10**	**1.81**
				$p_{trend} < 0.01$	
Duration (years) of exposure at high[◆] level					
None (0)	342 (31.3)	454 (39.8)	-----		
Ever: Highest at low[*] or medium[¶] levels[◊]	265 (24.3)	285 (25.1)	1.17	0.93	1.47
Short (0.1–2.3)	156 (14.3)	134 (11.7)	**1.58**	**1.19**	**2.09**
Moderate (2.4–7.4)	136 (12.5)	134 (11.7)	1.27	0.95	1.70
Long (7.5–74.1)	192 (17.6)	134 (11.7)	**1.45**	**1.10**	**1.91**
				$p_{trend} < 0.01$	
Weighted Duration (Years) – Equation (1)					
None (0)	342 (31.3)	454 (39.7)	-----		
Short (0.1–0.4)	234 (21.4)	229 (20.1)	**1.32**	**1.04**	**1.67**
Moderate (0.5–1.7)	233 (21.4)	229 (20.1)	1.27	0.99	1.61
Long (1.8–55.1)	282 (25.8)	229 (20.1)	**1.38**	**1.09**	**1.75**
				$p_{trend} < 0.01$	

Exposure Assessment	Cases (%)	Controls (%)	OR	95% CI	
Average Probability – Equation (2)					
None (0)	342 (31.3)	454 (39.7)	-----		
Low (0.01–0.02)	218 (20.0)	229 (20.1)	1.25	0.98	1.59
Medium (0.03–0.07)	255 (23.4)	229 (20.1)	**1.41**	**1.11**	**1.78**
High (0.08–0.88)	276 (25.3)	229 (20.1)	**1.31**	**1.03**	**1.66**
				p_{trend} = 0.01	

‡Adjusted for age, centre, education, ethnicity, smoking (pack-years). All p_{trend} values are calculated by treating ordinal categories as continuous values

†Maximum level classification, regardless of duration, is the maximum exposure level to which the participant was exposed across all occupations.

*Analysis for exposure at low level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ = (0.1 – 2.9%) in at least one job

¶Analysis for exposure at medium level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ = (3.0 – 8.9%) in at least one job

◆Analysis for exposure at high level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ ≥ 9% in at least one job

ΔTo ensure referent group are truly unexposed, a nuisance variable was created for the low-exposed group where value = 1, if highest duration at low level exposure, else 0

◊To ensure referent group are truly unexposed, a nuisance variable was created for the low/medium-exposed group where value = 1, if highest duration at low or medium level exposure, else 0

Table 3:

Polycyclic aromatic hydrocarbon exposure and breast cancer risk stratified by menopausal status[‡]

	Postmenopausal					Premenopausal					
Exposure Assessment	**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**Interaction**
Ever-Never: Any level											
Never	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Ever	445 (66.8)	384 (57.0)	**1.30**	**1.03**	**1.65**	304 (71.7)	303 (64.9)	1.32	0.98	1.78	
											$p > 0.9$
Ever-Never: At maximum level[†]											
Never	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Maximum level at low[*]	71 (10.7)	67 (09.9)	1.20	0.81	1.78	19 (04.5)	40 (08.6)	0.67	0.36	1.23	
Maximum level at medium[¶]	112 (16.8)	101 (15.0)	1.32	0.94	1.84	63 (14.9)	77 (16.5)	1.14	0.75	1.74	
Maximum level at high[◆]	262 (39.3)	216 (32.1)	**1.33**	**1.02**	**1.74**	222 (52.3)	186 (39.8)	**1.53**	**1.11**	**2.11**	
				$p_{trend} = 0.03$					$p_{trend} < 0.01$		$p_{trend} > 0.4$
Duration (years) of exposure at any level											
None (0)	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Short (0.1–4.2)	128 (19.2)	114 (16.9)	**1.47**	**1.07**	**2.02**	107 (25.2)	115 (24.6)	1.34	0.93	1.93	
Moderate (4.3–13.0)	154 (23.1)	134 (19.9)	1.30	0.96	1.77	102 (24.1)	96 (20.6)	1.39	0.95	2.03	
Long (13.1–82.2)	163 (24.5)	136 (20.2)	1.17	0.85	1.59	95 (22.4)	92 (19.7)	1.23	0.83	1.82	
				$p_{trend} > 0.2$					$p_{trend} > 0.2$		$p_{trend} > 0.8$
Duration (years) of exposure at medium[¶] or high[◆] levels											
None (0)	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Ever: Maximum at low level[Δ]	71 (10.7)	67 (10.0)	1.20	0.81	1.77	19 (04.5)	40 (08.6)	0.67	0.36	1.24	
Short (0.1–2.7)	106 (15.9)	95 (14.1)	**1.46**	**1.04**	**2.05**	97 (22.9)	99 (21.2)	1.32	0.91	1.93	
Moderate (2.8–9.0)	114 (17.1)	102 (15.1)	1.30	0.93	1.83	89 (21.0)	94 (20.1)	1.32	0.89	1.95	
Long (9.1–80.8)	154 (23.1)	120 (17.8)	1.24	0.90	1.71	99 (23.3)	70 (15.0)	**1.68**	**1.12**	**2.52**	
				$p_{trend} > 0.1$					$p_{trend} = 0.01$		$p_{trend} > 0.2$
Duration (years) of exposure at high level[◆]											

	Postmenopausal					Premenopausal					
Exposure Assessment	**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**Interaction**
None (0)	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Ever: Maximum at low [*] or medium [¶] levels [◊]	183 (27.5)	168 (24.9)	1.27	0.95	1.69	82 (19.3)	117 (25.1)	0.98	0.67	1.43	
Short (0.1–2.3)	75 (11.3)	60 (08.9)	**1.65**	**1.11**	**2.45**	81 (19.1)	74 (15.8)	1.49	0.99	2.24	
Moderate (2.4–7.4)	69 (10.4)	70 (10.4)	1.11	0.75	1.60	67 (15.8)	64 (13.7)	1.42	0.92	2.18	
Long (7.5–74.1)	118 (17.7)	86 (12.8)	1.29	0.90	1.84	74 (17.5)	48 (10.3)	**1.74**	**1.10**	**2.74**	
				$p_{trend} > 0.1$					$p_{trend} = 0.01$		$p_{trend} > 0.1$
Weighted Duration (Years) – Equation (1)											
None (0)	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Short (0.1–0.4)	155 (23.3)	127 (18.8)	**1.49**	**1.10**	**2.02**	79 (18.6)	102 (21.8)	1.06	0.72	1.56	
Moderate (0.5–1.7)	127 (19.1)	124 (18.4)	1.17	0.85	1.61	106 (25.0)	105 (22.5)	1.35	0.93	1.95	
Long (1.8–55.1)	163 (24.5)	133 (19.7)	**1.24**	**0.91**	**1.69**	119 (28.1)	95 (20.6)	**1.58**	**1.08**	**2.29**	
				$p_{trend} > 0.2$					$p_{trend} < 0.01$		$p_{trend} > 0.3$
Average Probability – Equation (2)											
None (0)	221 (33.2)	290 (43.0)	-----			120 (28.3)	164 (35.1)	-----			
Low (0.01–0.02)	149 (22.4)	142 (21.1)	1.30	0.96	1.76	69 (16.3)	87 (18.6)	1.12	0.74	1.68	
Medium (0.03–0.07)	146 (21.9)	116 (17.2)	**1.46**	**1.07**	**2.00**	109 (25.7)	113 (24.2)	1.31	0.91	1.90	
High (0.08–0.88)	150 (22.5)	126 (18.7)	1.14	0.82	1.57	126 (29.7)	103 (22.1)	**1.50**	**1.04**	**2.17**	
				$p_{trend} > 0.1$					$p_{trend} = 0.02$		$p_{trend} > 0.5$

[ǂ] Adjusted for age, centre, education, ethnicity, smoking (pack-years). All p_{trend} values are calculated by treating ordinal categories as continuous values

[†] Maximum level classification, regardless of duration, is the maximum exposure level to which the participant was exposed across all occupations.

[*] Analysis for exposure at low level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ = (0.1 – 2.9%) in at least one job

[¶] Analysis for exposure at medium level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ = (3.0 – 8.9%) in at least one job

[◆] Analysis for exposure at high level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ ≥ 9% in at least one job

[Δ] To ensure referent group are truly unexposed, a nuisance variable was created for the low-exposed group where value = 1, if highest duration at low level exposure, else 0

[◊] To ensure referent group are truly unexposed, a nuisance variable was created for the low/medium-exposed group where value = 1, if highest duration at low or medium level exposure, else 0

Table 4:

Exposure assessment to polycyclic aromatic hydrocarbons and breast cancer risk stratified by (first degree) family history of breast cancer[‡]

	No Family History					(First degree) Family History					
Exposure Assessment	**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**p-interaction**
Ever-Never: Any level											
Never	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Ever	594 (68.0)	597 (61.0)	**1.23**	**1.01**	**1.51**	155 (71.4)	90 (55.2)	**1.84**	**1.16**	**2.92**	
											p = 0.08
Ever-Never: At maximum level [†]											
Never	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Maximum level at low [*]	76 (08.7)	92 (09.4)	1.04	0.73	1.48	14 (06.4)	15 (09.2)	0.95	0.40	2.24	
Maximum level at medium [¶]	131 (15.0)	150 (15.3)	1.16	0.87	1.56	44 (20.3)	28 (17.2)	1.68	0.90	3.13	
Maximum level at high [◆]	387 (44.3)	355 (36.3)	**1.31**	**1.04**	**1.64**	97 (44.7)	47 (28.8)	**2.27**	**1.34**	**3.86**	
				p_{trend} = 0.02					p_{trend} < 0.01		p_{int}-trend = 0.03
Duration (years) of exposure at any level											
None (0)	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Short (0.1–4.2)	178 (20.4)	194 (19.8)	**1.31**	**1.01**	**1.71**	57 (26.2)	35 (21.5)	**1.95**	**1.09**	**3.48**	
Moderate (4.3–13.0)	202 (23.1)	202 (20.7)	1.22	0.94	1.59	54 (24.9)	28 (17.2)	**2.16**	**1.17**	**3.97**	
Long (13.1–82.2)	214 (24.5)	201 (20.5)	1.15	0.88	1.50	44 (20.3)	27 (16.5)	1.38	0.72	2.65	
				p_{trend} > 0.2					p_{trend} > 0.1		p_{int}-trend > 0.2
Duration (years) of exposure at medium [¶] or high [◆] levels											
None (0)	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Ever: Maximum at low level [Δ]	76 (08.7)	92 (09.4)	1.04	0.73	1.47	14 (06.4)	15 (09.2)	0.97	0.41	2.28	
Short (0.1–2.7)	159 (18.2)	163 (16.6)	**1.36**	**1.03**	**1.80**	44 (20.3)	31 (19.0)	1.64	0.90	3.00	
Moderate (2.8–9.0)	152 (17.4)	169 (17.3)	1.14	0.86	1.51	51 (23.5)	27 (16.6)	**2.24**	**1.20**	**4.18**	
Long (9.1–80.8)	207 (23.7)	173 (17.7)	1.29	0.98	1.70	46 (21.2)	17 (10.4)	**2.53**	**1.24**	**5.16**	
				p_{trend} = 0.09					p_{trend} < 0.01		p_{int}-trend = 0.01
Duration (years) of exposure at the high level [◆]											

	No Family History					(First degree) Family History					
Exposure Assessment	**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**Cases (%)**	**Controls (%)**	**OR**	**95% CI**		**p-interaction**
None (0)	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Ever: Maximum at low * or medium ¶ levels ◊	207 (23.7)	242 (24.7)	1.11	0.86	1.43	58 (26.7)	43 (26.4)	1.43	0.82	2.49	
Short (0.1–2.3)	121 (13.8)	114 (11.6)	**1.50**	**1.10**	**2.05**	35 (16.1)	20 (12.3)	1.94	0.98	3.82	
Moderate (2.4–7.4)	109 (12.5)	118 (12.1)	1.15	0.83	1.58	27 (12.5)	16 (09.8)	**2.31**	**1.07**	**5.01**	
Long (7.5–74.1)	157 (18.0)	123 (12.6)	1.29	0.95	1.75	35 (16.1)	11 (06.7)	**2.79**	**1.25**	**6.24**	
				$p_{trend} > 0.1$					$p_{trend} < 0.01$		p_{int}-trend = 0.03
Weighted Duration (Years) – Equation (1)											
None (0)	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Short (0.1–0.4)	181 (20.7)	193 (19.7)	1.25	0.96	1.63	53 (24.4)	36 (22.1)	1.66	0.94	2.94	
Moderate (0.5–1.7)	287 (21.4)	201 (20.5)	1.18	0.90	1.53	46 (21.2)	28 (17.2)	1.75	0.95	3.25	
Long (1.8–55.1)	226 (25.9)	203 (20.8)	1.25	0.97	1.63	56 (25.8)	26 (15.9)	**2.26**	**1.19**	**4.28**	
				$p_{trend} > 0.1$					$p_{trend} < 0.01$		p_{int}-trend = 0.06
Average Probability – Equation (2)											
None (0)	280 (32.0)	381 (39.0)	-----			62 (28.6)	73 (44.8)	-----			
Low (0.01–0.02)	165 (18.9)	191 (19.5)	1.18	0.90	1.55	53 (24.4)	38 (23.3)	1.57	0.89	2.76	
Medium (0.03–0.07)	212 (24.3)	202 (20.6)	**1.36**	**1.05**	**1.76**	43 (19.8)	27 (16.6)	1.71	0.91	3.20	
High (0.08–0.88)	217 (24.8)	204 (20.9)	1.14	0.87	1.49	59 (27.2)	25 (15.3)	**2.55**	**1.34**	**4.84**	
				$p_{trend} > 0.1$					$p_{trend} < 0.01$		p_{int}-trend = 0.03

≠ Adjusted for age, centre, education, ethnicity, smoking (pack-years). All p_{trend} values are calculated by treating ordinal categories as continuous values

† Maximum level classification, regardless of duration, is the maximum exposure level to which the participant was exposed across all occupations.

* Analysis for exposure at low level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ = (0.1 – 2.9%) in at least one job

¶ Analysis for exposure at medium level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ = (3.0 – 8.9%) in at least one job

◆ Analysis for exposure at high level (estimated probability of exposure above 0.2 mg/m^3 of coal tar pitch volatiles) is θ ≥ 9% in at least one job

Δ To ensure referent group are truly unexposed, a nuisance variable was created for the low-exposed group where value = 1, if highest duration at low level exposure, else 0

◊ To ensure referent group are truly unexposed, a nuisance variable was created for the low/medium-exposed group where value = 1, if highest duration at low or medium level exposure, else 0