Postmenopausal breast cancer and occupational exposures

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ABSTRACT
Objective To determine whether exposures in the workplace to organic solvents and to other agents, such as polycyclic aromatic hydrocarbons, are associated with increased risks of developing postmenopausal breast cancer.
Methods Between 1996 and 1997 a case–control study was conducted in Montreal, Quebec. Cases comprised 556 women, aged 50–75 years, with incident malignant breast cancer, and their controls were 613 women with other cancers, frequency matched for age, date of diagnosis and hospital. An expert team of chemists and industrial hygienists translated their job histories into exposure to about 300 agents.
Results Odds ratios (ORs) were increased for the usual risk factors for breast cancer and, adjusting for these, risks increased with occupational exposure to several agents, and were highest for exposures occurring before age 36 years. Increased ORs were found for each 10-year increment in duration of exposure, before age 36 years (OR<36, to aromatic fibres (OR<36=7.69) and to nylon fibres (OR<36=1.99). For oestrogen-positive and progesterone-negative tumours, the OR doubled or more for exposure to organic solvents that metabolise into reactive oxygen species, and to aromatic fibres. A threefold increase was found for oestrogen- and progesterone-positive tumours, with exposure to polycyclic aromatic hydrocarbons from petroleum sources.
Conclusion Certain occupational exposures appear to increase the risk of developing postmenopausal breast cancer, although some findings might be due to chance or to undetected bias. Our findings are consistent with the hypothesis that breast tissue is more sensitive to adverse effects if exposure occurs when breast cells are still proliferating. More refined analyses, adjusting for hormonal receptor subtypes and studies focusing on certain chemical exposures are required to further our understanding of the role of chemicals in the development of breast cancer.

Over the past 30 years, the incidence of female breast cancer in most developed countries has increased dramatically,1 although it appears to have started recently to decline in the United States2 and in Canada,3 but not in the United Kingdom.4 In Canada, breast cancer accounts for an estimated 28% of all new cases of cancer and is the second leading cause of cancer death in women.5 Possible explanations for the increase in incidence rates include diagnosis of smaller slow-growing breast tumours,2 and secular changes in risk factors influencing hormonal metabolism,6 including the intake of alcohol6 and tobacco.7 Different patterns of risk factors have been reported recently according to hormonal receptor status, suggesting different aetiologies for distinctive types of tumours.8 Environmental and occupational agents may also be contributing factors in the aetiology of breast cancer, especially exposures to polycyclic aromatic hydrocarbons (PAHs),9 organochlorines,10 polychlorinated biphenyls11 (although not consistently so12), extremely low-frequency electromagnetic fields,13 circadian disruption, including night shift work,14 and organic solvents.15 Many of these exposures are carcinogenic in animal models,11 16 Various mechanisms of carcinogenicity have been proposed; for example, PAHs have been shown to form DNA adducts,9 and organic solvents could be converted by breast cells into reactive oxygen species (involving free radicals and epoxides), and exert local direct effects leading to cancer induction.17 Hypothetical mechanisms of action for organochlorines and PAHs also involve oestrogen-mimicking properties, such as increased cell proliferation.11

What this paper adds
Main messages
• Occupational and environmental agents may be contributing factors in the aetiology of breast cancer.
• Occupational exposure to acrylic and nylon fibres, and to polycyclic aromatic hydrocarbons may increase the risk of developing postmenopausal breast cancer.
• For breast tumours with certain hormonal receptor subtypes, exposure to organic solvents that metabolise into reactive oxygen species and to polycyclic aromatic hydrocarbons may also be associated with an increased risk.
• The risks appear to be higher when exposures occur at a younger age.

Policy implications
• Our findings are consistent with the hypothesis that breast tissue is more sensitive to adverse effects if exposure occurs when breast cells are still proliferating. Young female workers should be considered as a sensitive population to occupational and, possibly, environmental exposures.

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a few years ago we found few high-quality studies. Since then, there have been a handful of new studies that have shown increased risks associated with occupational exposures to organic solvents or to holding a job with probable exposure to organic solvents, and to other chemical exposures such as ethylene oxide and aromatic hydrocarbons.

To further our understanding of the aetiology of breast cancer, we conducted between 1996 and 1997 a hospital-based case-control study in all hospitals in Montreal, Quebec, that treated female breast cancer. The main objectives were to determine whether occupational exposures to organic solvents, and to other agents associated with breast cancer risk in other studies—such as PAHs, confer a higher risk of developing a primary, invasive breast cancer in postmenopausal women; secondary objectives were to determine whether risk differed with age at the time of exposure and with hormonal status of the breast tumour.

MATERIALS AND METHODS

Study population
Eligible cases comprised women who were diagnosed for the first time in 1996 and 1997, between ages 50 and 75 years, with a primary, malignant breast neoplasm (International Classification of Diseases, ninth revision (ICD-9), code 174), and residing in the greater Montreal area. Coverage of the target population was complete, as study subjects were identified from records of pathology departments and cancer registries from the 18 hospitals in the area that provided diagnosis and/or treatment for breast cancer. Control subjects included newly diagnosed cases of breast cancer, postmenopausal status was classified according to the WHO definition: women over the age of 50 who ceased menstruation naturally in the 12 months before the interview or who ceased menstruating after a bilateral oophorectomy; women who were still menstruating but had used hormone replacement therapy to alleviate symptoms of the menopause; and women who had a simple hysterectomy without oophorectomy and reported using hormone replacement therapy.

The research protocol was approved by the ethics committees of all participating hospitals and affiliated universities, and informed consent was obtained from participating subjects.

Data collection
Telephone or in-person interviews were conducted 1–3 months after diagnosis. If a subject was too ill to participate directly, interviews were conducted with surrogate respondents (mostly spouses).

The first part of the interview elicited details of known or suspected risk factors, including sociodemographic factors, gynaecological and obstetric histories, medical and familial histories, use of oral contraceptives and hormonal therapy, history of alcohol and smoking consumption, physical activity, diet, hobbies and places of residence. Using a standard methodology developed by Siemiatycki and coworkers,20, 21 interviewers used a structured set of general and job-specific questionnaires (eg, for hairdressers, nurses, textile workers, etc) and they were trained to probe for details for each occupation that the subject had ever had in her working lifetime.30

Estimation of chemical exposures

The methodology to attribute occupational exposures from the detailed lifetime job histories, as developed by Siemiatycki and collaborators.20, 21 was used to estimate occupational exposures. Despite the fact that this methodology was developed 30 years ago, it remains state-of-the-art and is used in many centres.31–33 Brieﬂy, all jobs for each subject were translated into a set of exposure indices for about 500 chemical and physical agents by a team of experienced industrial hygienists and chemists who were unaware of the disease status of subjects. The method has been shown to have high inter-rater agreement for the presence or absence of chemicals (k=0.67–0.80).34, 35 When experienced chemical coders and interviewers are available, this procedure is believed to be better than other systems.36 Some agents were grouped into broader categories according to algorithms developed by us. For example, exposures to gasoline, diesel and jet fuel engine emissions or mineral spirits were also recoded as exposures to alkanes with 5–17 carbon chains (alkanes (C5–C17)); exposures to benzene, toluene, xylene and styrene from different sources were also recoded as exposures to monoaromatic hydrocarbons (MAHs); and more than 20 compounds (eg, carbon black, petroleum soot, jet fuel engine emissions, oil-based cutting ﬂuids, etc) were recoded as containing PAHs from petroleum.

For each agent judged to be present, the team coded physical aspect, average duration of exposure (in hours) in a working day, percentage of the working days exposed during the period, conﬁdence that there was actual exposure to each agent, using a four-point ordinal scale (probably no occupational exposure, and ‘low’, ‘medium’ and ‘high’ conﬁdence of exposure), and level of intensity. Intensity was assessed on a rank-ordered scale of low, medium and high intensity. Exposures up to the level expected to be found in the general environment were deemed to be ‘unexposed’. Two members of the team coded each file and then reached a ﬁnal consensus on the attribution of exposure. A complete recoding of the ﬁles was carried out afterwards to ensure consistency.

Exposure indices

Two additional indices were developed to assess our prior hypothesis relating exposure to organic solvents and breast cancer.16 The ‘organic solvents’ category included all volatile organic liquids, even if they were not used as solvents (eg, benzene used as a reagent). The ‘solvents with reactive metabolites’ category comprised benzene, carbon tetrachloride, chlorobenzene, 1,1-dichloroethane, methylene chloride, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, styrene, vinyl chloride, xylene, ethylene dibromide, ethylene dichloride, chlorinated alkanes and chlorinated alkenes.16

Data handling and statistical analysis

We included for these analyses only the chemical exposures that were attributed to at least 5% of cases or referents and rated by the coding team with a medium or high conﬁdence of occurrence (22 of a possible 300 agents). Binary indices were deﬁned as not occupationally exposed, as compared with working in an exposed job. Additionally, we deﬁned an index reflecting
‘substantial exposure’ for jobs entailing ≥5 years of exposure at medium or high levels of intensity, ‘non-substantial exposure’ for jobs with <5 years of exposure at medium or high levels of intensity, but still ≥5 years of exposure at any intensity, and finally, we pooled all the other exposures. Continuous indices were also computed by summing up the number of hours of exposure, at any level of intensity. For both binary and continuous indices, three time windows of exposure were used: lifetime exposures; excluding exposures that occurred ≤10 years before diagnosis; and exposures before the age of 56 years (the period during which breast tissue may be more susceptible to exogenous insults, as female breast cells continue to develop until that age37; hereafter referred to as ‘early exposures’).

Hormonal receptor status was categorised as positive or negative for oestrogen (ER+ or ER−) and/or progesterone (PR+ or PR−) receptors, as provided in the pathology reports.

Unconditional logistic regression was used to estimate ORs and associated 95% CIs. In order to assess patterns of exposure—response and to provide more precise control of confounding for continuous covariates, natural cubic splines were used with four degrees of freedom,38 as implemented in S-PLUS. The response functions were inspected visually and statistically. In order not to lose subjects because of missing values of continuous non-occupational covariates, these potential confounding variables were modelled as categorical functions whereby missing values were assigned to a ‘missing’ category. The remaining categories were defined after inspection of the response function by setting cut-off points such that the ORs within each category were approximately the same. In the final model, only age was treated continuously and the best fitting function was linear.

Fully adjusted models included variables accepted or suspected to be associated with breast cancer risk or distributed unequally between cases and referents: age at diagnosis; family history; education; ethnicity; age at menarche; age at first full-term pregnancy; total duration of breast feeding; oral contraceptive use; duration of hormone replacement therapy; alcohol drinking status. For oral contraceptive use, the risk was higher for short-term users. Having a first full-term pregnancy after age 30 years was associated with a slightly elevated non-significant risk, whereas having had three children or more and having breastfed for more than 12 months showed a slightly decreased non-significant risk.

Organic solvents

Table 1 shows associations for the composite indices of exposure to organic solvents. There was little evidence of positive associations, although the ORs were generally larger when exposures occurred before age 56 years than during other time periods. Table 2 shows ORs for each 10-year increment in duration of exposure for those coded at medium or high confidence of exposure to organic solvents, both for lifetime exposure and for exposures before age 56 years, and according to hormonal phenotype. Except for ER+/PR− tumours, ORs increased monotonically with duration of exposure, although the CIs were broad and included the null value. Again, we found larger ORs for exposures that occurred before the age of 56 years than for other time periods. For all tumour types combined, we found increases in risk for organic solvents with reactive metabolites but the CIs included the null value and were quite broad (lifetime exposures: OR10-yr increase=1.14 (95% CI 0.80 to 1.62); before age 56 years: OR10-yr increase=1.30 (95% CI 0.65 to 2.60). ORs were systematically higher for ER+/PR− tumours than for other hormonal phenotypes, in particular for exposures to organic solvents with reactive metabolites before age 56 years (OR<56=3.31; 95% CI 1.07 to 10.20).

Other chemical exposures

Table 3 shows associations for non-substantial and substantial exposures to 12 selected substances or groups of substances. We found increased ORs with non-substantial exposure to acrylic fibres, and to PAHs from petroleum. Table 4 shows ORs per 10-year increase in duration of exposure to these 12 substances, for those coded at medium or high confidence of occurrence, according to lifetime exposure, and exposures before age 56 years. We also show selected findings by hormonal phenotype. (The online Appendix table 2 shows results for all agents.) Essentially, null associations were found for aliphatic alcohols, aliphatic aldehydes, alkanes (C5–C17 and C18+), ammonia, calcium carbonate, insecticides, leaded and unleaded engine emissions, pesticides, polyester fibres and toluene.

Seventy-six per cent of cases were diagnosed with an infiltrating duct carcinoma, 11% with lobular carcinomas and 5% with adeno carcinomas. The most common sites of cancer in the control series were geriutourinary organs (ICD-9 codes 150–159, 41%), other digestive system and peritoneum (ICD-9 codes 150–159, 37%), and eye and thyroid gland (ICD-9 codes 190–199, 9%), and bones, connective tissue and skin (ICD-9 codes 170–179, 5%). The distribution of hormonal receptor status among the cases was: oestrogen positive (ER+), 395; oestrogen negative (ER−), 100; missing, oestrogen, 61 (11.0%); progesterone positive (PR+), 326; progesterone negative (PR−), 10; missing, progesterone, 64 (11.5%). The joint distribution of oestrogen/progesterone status (ER/PR) was: 310 ER+/PR+ cases (63.0%); 84 ER−/PR− cases (17.1%); 82 ER+/PR− cases (16.7%) and 16 ER−/PR+ cases (5.5%).
We found associations for early exposures to PAHs from petroleum sources and to PAHs from any source. As well, exposures to wool and to certain synthetic fibres were associated with postmenopausal breast cancer: (a) acrylic fibres conferred a twofold increased risk per 10-year increase in lifetime exposure, and a sevenfold increased risk if exposure occurred before age 36 years; (b) nylon fibres showed a twofold elevated risk for early exposures; (c) rayon fibres were associated with increased risk for lifetime exposure (OR10-yr increase = 1.51; 95% CI 1.00 to 2.25) and higher risks with early exposures and (d) synthetic fibres and wool fibres showed elevated risks especially for early exposure. These fibres are mostly found in the textile industry and are somewhat correlated with each other. Adjustment for individual fibre types tended to slightly lower the OR10-yr increase for most fibres but the association with acrylic fibres remained (data not shown).

Adjustment for extremely low-frequency electromagnetic fields exposure, quite common in the textile industry, also lowered the ORs for several fibres, but did not appreciably modify the association with acrylic, nylon and wool fibres (data not shown).

An association was also found with early exposures to carbon monoxide (OR10-yr increase <5 years = 1.66; 95% CI 1.20 to 2.70), but no association was found for lifetime exposure. Exposure to inks showed increased risks, although the CIs were broad, especially with early exposures: OR10-yr increase <5 years = 2.89 (95% CI 0.96 to 8.71).

We also conducted analyses for these 12 chemicals by hormonal phenotype. The right-hand section of table 4 presents the elevated OR10-yr increase (see online Appendix table 2 for complete results). Data for the ER−/PR+ tumours are not reported because of small numbers (n=16). PAHs from petroleum were associated with elevated ORs in ER+/PR+ tumours for both early and lifetime exposures. Risks were also increased with specific hormonal phenotypes for many of the synthetic fibres: (a) lifetime and early exposure to acrylic fibres among cases classified as ER+/PR− status and early exposures for ER+/PR− status; (b) early exposure to nylon fibres and synthetic fibres among cases with ER+/PR+ status; (c) lifetime exposures to rayon fibres among cases with ER+/PR− status. Two other chemicals also showed associations among the ER+/PR− phenotype: lifetime exposure to MAHs and early exposure to carbon monoxide.

### DISCUSSION

We found that occupational exposure, before age 36 years, to organic solvents that have reactive metabolites conferred increased risks of postmenopausal breast cancer. For tumours that were oestrogen positive and progesterone negative (ER+/PR−), the risk tripled for each 10-year increase in duration of exposure. For the same tumour type, the risk more than doubled for each 10-year increase in duration of exposure to MAHs and to acrylic and rayon fibres. Among women with early exposures, acrylic fibres, carbon monoxide, nylon fibres and wool fibres minimally doubled the risk of postmenopausal breast cancer, and exposure to PAHs from petroleum tripled the risk for ER+/PR+ tumours. As in any study, some or all of these associations may have arisen simply by chance.

This is one of the few comprehensive occupational studies of female breast cancer with high-quality data on occupational exposures. Although hospital based, it had 100% coverage of the base population: patients with selected sites of cancer from all hospitals of the area were invited to participate as controls, and we excluded patients residing outside the area, ensuring that both study groups came from the same source population. All cases and controls were confirmed histologically. Our response rates were high and it is likely that the use of cancer controls minimised potential recall biases, as compared with using general population controls. It is also possible that patients with cancer may recall their exposures differently according to cancer type, and risks may be underestimated if some of the control cancer sites were also associated with certain occupational exposures. To minimise these potential biases, we selected a wide array of cancer sites, after excluding sites reported to be associated with exposure to solvents.

We obtained from both cases and controls comprehensive information on potential confounding variables and we found elevated risks for the principal accepted risk factors for breast cancer, suggesting little selection bias. The distribution of tumour types and of joint oestrogen and progesterone receptor status of our cases was also similar to that reported elsewhere. Lastly, the assessments of occupational exposures by the team of industrial hygienists and chemists, using detailed lifetime occupational histories, is considered to be state-of-the-art and provides more valid estimates of risk to exposures than methods.
Only replication can illuminate recent studies.

<table>
<thead>
<tr>
<th>Organic solvents with reactive metabolites</th>
<th>Lifetime exposure</th>
<th>OR (95% CI)</th>
<th>Exposure before age 36 years</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volatile organic liquids</td>
<td>1.12 (0.81 to 1.53)</td>
<td>1.26 (0.98 to 1.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic solvents with reactive metabolites</td>
<td>1.22 (0.89 to 1.69)</td>
<td>1.56 (1.17 to 2.06)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, family history, age at oophorectomy, education, ethnicity, age at menarche, oral contraceptive use, hormone therapy use, total duration of breastfeeding, smoking status, alcohol consumption status, body mass index, age at first full-term pregnancy (≥35 weeks) and proxy respondent status.

As mentioned in the ‘Methods’, for the purposes of the paper, we expanded the usual definition of a positive association as a means of further exploring the data. A main problem with this type of study is the low prevalence of exposure, and this reduces power. Our purpose here is not to reach conclusions about possible associations but rather to present what we think may be possible leads that would allow other researchers to build on our work as well as to provide sufficient information to conduct summaries across studies so that more robust conclusions can be made. We reiterate that some positive results might be chance findings; we chose not to use any Bonferroni-like procedures for correcting the nominal level of statistical significance as power would be reduced considerably. Only replication can illuminate the true nature of these findings, and with this in mind we turn to a discussion of specific findings.

### Organic solvents, monoaromatic hydrocarbons and inks

Increased risks were found with lifetime exposure to monoaromatic hydrocarbons (a chemical class that includes benzene and phenyl-containing chemicals), and to early exposures to solvents with reactive metabolites, including many chemicals that are mammary carcinogens in animals (eg, 1,1-dichloroethane, 1,2-dichloropropane, methylene chloride, nitromethane, 1,2,3-trichloropropane, 1,2-dibromomethane, 1,2-dichloroethane). Similar findings have been reported elsewhere, but not in one other study. These associations are consistent with the hypothesis that organic solvents with reactive metabolites may increase the risk of breast cancer among postmenopausal women, and perhaps even more so if women are exposed before breast cells start their involution.

Exposure to inks was also associated with an increased risk when women were exposed before age 36 years. Inks are composed of pigments, a vehicle (solvent) and additives (brighteners, driers, plasticisers, etc) and although printing inks are considered ‘not classifiable as to carcinogenicity to humans’ (group 3 of the International Agency for Research on Cancer), occupational exposures in printing processes are classified as ‘possibly carcinogenic to humans’, or group 2B. Recent studies have reported increased risks of breast cancer among printers and chemical workers.

### Polycyclic aromatic hydrocarbons

Increased risks were found for exposure to PAHs, especially to PAHs derived from petroleum, and among women with early exposures. A few studies showed increased risks with occupational exposure to PAHs among pre- and postmenopausal women, with an approximately 30% increases in risk. Some PAHs are known carcinogens, while a few others are classified as probably or possibly carcinogenic to humans. PAHs derive from incomplete combustion of organic material and their concentrations are influenced particularly by industrial and urban air pollution. The association with carbon monoxide may well be a surrogate for exposure to exhausts from combustion sources.

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**Table 2. ORs and 95% CI for lifetime exposure and for exposure before age 36 years, per 10-year increase of occupational exposure to any intensity of two organicsolvents indices, according to tumour hormone phenotypes**

<table>
<thead>
<tr>
<th>Tumour hormone phenotype</th>
<th>All tumours</th>
<th>ER+/PR+</th>
<th>ER+/PR-</th>
<th>ER-/PR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime exposure ORs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>1.12</td>
<td>1.22</td>
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<tr>
<td>95% CI</td>
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<td>(0.89 to 1.69)</td>
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<tr>
<td>Exposure before age 36 years ORs</td>
<td>1.26</td>
<td>1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>1.17</td>
<td>1.54</td>
<td></td>
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</tbody>
</table>

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**Note:** ORs and 95% CI for lifetime exposure and for exposure before age 36 years, per 10-year increase of occupational exposure to any intensity of two organicsolvents indices, according to tumour hormone phenotypes. ER+/PR+, oestrogen and progesterone receptor-positive tumours; ER+/PR-, oestrogen and progesterone receptor-negative tumours; ER+/PR+, oestrogen receptor-positive and progesterone receptor-negative tumours. **Postmenopausal breast cancer, Montreal, Canada, 1996**
Synthetic fibres and other textile fibres
Exposures to synthetic fibres, in particular acrylic, rayon and nylon fibres, but also to wood fibres, were found to increase risk of cancer.

One study has reported a non-significant increased risk of breast cancer with exposure to wool dust, and increased risks have been reported in some studies among textile workers, but not in others.

We did not find any published study on associations between breast cancer and synthetic fibres as a group or for individual types of synthetic fibres. Synthetic fibres are treated with several chemicals such as flame retardants (all from the organophosphate family), deluster ing agents (titanium dioxide) and, of course, dyes, some of which have oestrogenic properties and some that are recognised animal carcinogens.

Textile workers are also exposed to organic solvents and to electromagnetic fields that may respectively or concomitantly be associated with increased risks of breast cancer. Adjustment for individual fibres and for extremely low-frequency electromagnetic fields, both common in the textile industry, did not appreciably modify the results in our study (data not shown).

Hormonal receptor status
A few authors have reported heterogeneity in risks associated with ‘accepted’ risk factors according to hormonal receptor status of breast tumours, suggesting the existence of different types of breast tumours possibly having different aetiologies and aetiological pathways.

If chemicals exert their effects through a hormonal mediated pathway, they would be expected to show, for tumours with a given hormonal receptor status, patterns of association similar to those of endogenous hormones. The increases found with exposures to PAHs and synthetic fibres among ER+/PR+ tumours are consistent with this literature.

Table 3 ORs and 95% CI for composite binary indices of occupational exposure to medium or high levels of selected substances, postmenopausal breast cancer, Montreal, Canada, 1996–7

Table 4 ORs and 95% CI for lifetime and exposure before age 36 years, per 10-year increase of occupational exposure to any intensity of selected substances, and selected findings* by hormonal phenotypes† postmenopausal breast cancer, Montreal, Canada, 1996–7.

*Substantial exposure, >5 years of exposure at medium or high levels of intensity; non-substantial exposure, <5 years of exposure at medium or high levels of intensity, but still >5 years of exposure at any intensity.

†Adjusted for age, family history, age at oophorectomy, education, ethnicity, age at menarche, oral contraceptive use, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, alcohol consumption status, body mass index, age at first full-term pregnancy (±5 weeks) and proxy respondent status.

MAHs, monoaromatic hydrocarbons; PAHs, polycyclic aromatic hydrocarbons.
CONCLUSION
Our findings are generally consistent with the hypothesis that breast tissue is more sensitive to adverse effects when exposure occurs when breast cells are still proliferating (before the fourth decade of life). More refined analyses and adjusting for hormonal receptor subtypes, and studies focusing on certain chemical exposures are needed to elucidate the role of occupational chemicals and postmenopausal breast cancer.

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Contributors
All of the authors participated in the preparation of the paper and have approved the submitted version. FL and MSG designed the study, directed it and are responsible for the analysis and paper preparation. MF-P supervised data verification, review and interpretation of the results. MSG supervised occupational history data collection and directed the exposure coding.

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Competing interests
None.

Ethics approval
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