Air pollution Exposure And Mammographic Breast Density In Tehran, Iran

Bita Eslami  
Tehran University of Medical Sciences

Sadaf Alipour  
Tehran University of Medical Sciences

Ramesh Omranipour  
Tehran University of Medical Sciences

Kazem Naddafi  
Tehran University of Medical Sciences

Mohammad Mehdi Naghizadeh  
Fasa University of Medical Science

Mansour Shamsipour  
Tehran University of Medical Sciences

Arvin Aryan  
Tehran University of Medical Sciences

Mahboubeh Abedi  
Tehran University of Medical Sciences

Leila Bayani  
Tehran University of Medical Sciences

Mohammad Sadegh Hassanvand (bdrc@tums.ac.ir)  
Tehran University of Medical Sciences  https://orcid.org/0000-0003-2916-5370

Research Article

Keywords: Breast Density, Mammography, Air Pollutants, Nitrogen Dioxide, Carbon monoxide.

Posted Date: October 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-988346/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: Air pollution is one of the major public health challenges in many parts of the world possibly has an association with breast cancer. However, the mechanism is still unclear. This study aimed to find an association between exposure to six criteria ambient air pollutants ($\text{PM}_{2.5}$, $\text{PM}_{10}$, $\text{SO}_2$, $\text{NO}_2$, $\text{O}_3$, and $\text{CO}$) and mammographic breast density (MBD), as one of the strongest predictors for developing breast cancer, in women living in Tehran, Iran.

Methods: Participants were selected from women attending two university hospitals for screening mammography from 2019 to 2021. Breast density was rated by two expert radiologists. Individual exposures to 3-years ambient air pollution levels at the residence were estimated.

Results: The final analysis in 791 eligible women showed that low and high breast density was detected in 34.8% and 62.2% of participants, respectively. Logistic regression analysis after considering all possible confounding factors represented that an increase in 10 units of $\text{NO}_2$ (ppb) exposure was associated with an increased risk of breast density with an OR equal to 1.47 (95% CI: 1.10 to 1.97). Furthermore, $\text{CO}$ level was associated with a decreasing breast density (OR = 0.33, 95% CI = 0.17 to 0.64). None of the other pollutants were associated with breast density.

Conclusion: MBD was associated with higher levels of ambient air $\text{NO}_2$ and lower levels of $\text{CO}$. Perhaps MBD monitoring as an available tool in each population, can help the prediction of future breast cancer occurrence and finding the high-risk geographic areas.

Background

Air pollution is one of the major public health challenges in many parts of the world and in large cities. Ambient air pollution is a mixture of different pollutants originating from natural and anthropogenic sources and the International Agency for Research on Cancer (IARC) classified it as Group 1 carcinogenic to humans (1). Several studies showed that short-and log-term exposure to air pollution can cause many chronic and acute health effects. Numerous studies reported that long-term exposure to outdoor air pollution caused globally around 4.24 million premature deaths annually (2–5).

Breast cancer is one of the worldwide leading causes of mortality and morbidity, and according to a report of GLOBOCAN in 2018 accounts for more than 11.6% of all female cancers; while the disease burden of breast cancer shows an increasing trend in some populations (6). Because this disease imposes a heavy burden on the health system, more preventive efforts are necessary and further investigation should explore the underlying reasons for these epidemiological trends. Ecologic studies suggest that breast cancer risk is elevated in urban areas with high levels of air pollution compared to rural areas (7, 8). Air pollution contains many carcinogens and other compounds that may act as endocrine disruptors, and air pollution exposure has been globally linked to many cancers such as lung, breast, and bladder cancer (9). In 1979 Hill and Winder found that inhaled toxicants (nicotine and
cotinine) were detectable in breast fluid after 30 minutes of smoking (10). Thus, toxic chemicals can reach the breast tissue and have possibly some impacts on it.

A systematic review and meta-analysis in 2021 investigated whether high levels of air pollution exposure were related to increased breast cancer risk (11). This study showed that NO\textsubscript{2} had a "moderate level of evidence" and that PM\textsubscript{2.5} and PM\textsubscript{10} have an "inadequate level of evidence" for supporting their association with breast cancer risk. Also, the biological mechanism of the effects of air pollutants on breast cancer still remains unknown (11).

Mammographic breast density (MBD) is one of the strongest predictors and biomarkers for developing breast cancer (12). Growing evidence suggests that environmental risk factors such as xenoestrogens [(Bisphenol-A (BPA)] and metalloestrogens (lead, cobalt, and magnesium) have a direct association with MBD (13, 14). However, one study has reported a reverse association between serum levels of Polychlorinated biphenyl (PCBs) as a xenoestrogen and MBD (15). Limited studies evaluated the association between MBD and air pollution exposure, which had also inconsistent results (16–19). To draw risk-reducing strategies for breast cancer, studying the impacts of ambient air pollutants on breast density may provide valuable data for monitoring and etiologic factors. Previous studies had limitations in the assessment of the exposure, in adjusting confounding variables, and in outcome ascertainment to find a causal relationship; therefore further studies have been recommended (11).

Tehran as the capital of Iran is a megacity with about 10 million residents and air pollution is a major environmental challenge in this city. The people of Tehran are more exposed to high levels of ambient air pollution, to the point where government and non-government offices are sometimes closed due to the severity of air pollution (3, 20). Therefore, the present study was designed to investigate whether there is an association between exposure to six criteria ambient air pollutants (Nitrogen dioxide (NO\textsubscript{2}), Sulfur dioxide (SO\textsubscript{2}), Carbon monoxide (CO), Ozone (O\textsubscript{3}), and Particulate matter (PM) \textsubscript{2.5, 10}) and MBD in women living in Tehran, Iran.

**Methods**

**Study design and participants**

This study was designed as a cross-sectional study; participants were selected from women attending two university hospitals affiliated to Tehran University of Medical Sciences, Tehran, Iran, for screening mammography from 2019 to 2021. The study was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1398.897), and all participants have signed an informed consent. All methods have been performed in accordance with the relevant principles of the Declaration of Helsinki.

Criteria for inclusion in the study were at least 3 years residency in the capital city of Iran (Tehran) and having the ability to fill questionnaires. Exclusion criteria included suspicion for malignancy in the current
mammography and an imprecise address.

**Data Collection**

Participants were asked to fill a questionnaire that captured demographic information, self-reported age, weight, height, reproductive history, menopause status, smoking history (active and passive), history of oral contraceptive (OCP) use, current use of hormone replacement therapy, and familial history of breast and ovarian cancer. All women who either had a current or previous history of active and passive (second hand) smoking were defined as having a positive exposure to smoke. Menopause was defined as cessation of the menstrual period at least one year sooner, women were stratified into premenopausal and postmenopausal status. Furthermore, we gathered information about current aspirin and metformin use and consumption duration in each woman. Routine use of supplements including vitamin D, calcium, Vitamin E, Omega 3, and Evening Primrose oil were also recorded.

One expert radiologist reported the breast density in each center. In order to decrease both intra- and interreader variability, the mammographic breast density was checked by a third radiologist. Radiologists rated MBD according to the American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS) classification into four categories: almost entirely fatty (BI-RADS 1), scattered areas of fibro glandular density (BI-RADS 2), heterogeneously dense (BI-RADS 3), and extremely dense (BI-RADS 4) (21). We categorized MBD into low density (ACR 1 and 2) and high density (ACR 3 and 4).

The exact address of residence of the participants in the recent 3 years and the telephone number of that place were recorded. Also, in the employed women, the address of their place of work and the hours of their attendance to work were recorded.

**Air pollution exposure assessment**

In this study, estimating the exposure of participants to ambient criteria air pollution was done in the following three steps:

1. Outdoor air quality data gathering from fixed monitoring stations belong to Tehran Air Quality Control Company.

2. Data cleaning of air quality monitoring stations in order to outlier data detection.
3. Individual long-term exposure assessment using air quality data and inverse distance weighting (IDW) approach.

**Air quality data gathering**

Real time hourly ambient air quality in Tehran city is monitored by fixed monitoring stations. In Tehran city, Air Quality Control Company (AQCC) affiliated to the Tehran Municipality is responsible for monitoring criteria air pollutant (PM$_{2.5}$, PM$_{10}$, NO$_2$, O$_3$, SO$_2$, and CO). At the time of this study in 2020, there were 22 monitoring stations in Tehran belonged to the AQCC. Considering that the data of the AQCC stations are available on an hourly basis and are publicly available online, and that these monitoring
stations are spatially located in all districts of Tehran city, therefore we used the data obtained from air quality monitoring stations belonged to AQCC in this study.

Finally, hourly data of six outdoor criteria air pollutants for the 3-years residency of participants were obtained from the website of AQCC (Available at: http://airnow.tehran.ir/home/DataArchive.aspx).

**Air quality data processing**

Data quality control is the most important part of air quality studies and estimating health effects. Data quality assurance was performed according to international organization guidelines such as World Health Organization (WHO), Environmental Protection Agency (EPA), and the European Union (22–24). Due to numerous operational and calibration problems related to air pollutant measuring stations, outlier detection and data cleaning from monitoring stations is very important and the results would have insufficient scientific validity if this step is omitted.

In the present study, first the data of all monitoring stations were obtained and then hourly data coverage of each pollutant in each station during the three years was determined. Included monitoring stations were only stations with ≥75% completeness of the total hours during the study period (22, 24). Then, in order to outlier data detection, the modified Z-score approach proposed by some researchers for this purpose was used (3, 23, 25, 26). Briefly, in order to identify outlier data, the following steps were used:

Calculating the Z score for each hourly data at each station using the following equation:

\[
Z = \frac{(\text{Concentration})_{\text{Hourly}} - (\text{Concentration})_{\text{Annual}}}{\text{SD of annual concentrations}}
\]

Calculating the following four conditions:

\[
Z_1 = |Z| > 4
\]

\[
Z_2 = (Z_t - Z_{t-1}) > 6
\]

\[
Z_3 = \left( \frac{Z_t}{\text{RM3}(Z_t)} \right) > 1.5
\]

\[
Z_4 = \frac{(Z_t - Z_{t-1})}{\text{City}(Z_t - Z_{t-1})} > 2
\]

Finally, the air quality data were detected as an outlier data and removed if they meet four above-mentioned conditions.

**Individual long-term exposure assessment**

To determine the long-term exposure of each participant to ambient air pollutants, the exact address according to the area, place, street, and alley in each year was obtained. In working women, if the place of work and living were different, the area and time spent in that area were also considered. Then, according
to the location of monitoring stations and the location of the study subject, three of the nearest included air quality monitoring stations were identified for each participant and using the average annual data and IDW method, the 3-year annual mean of exposure was estimated as long-term exposure for each study subject.

**Statistical analysis**

Data were presented with mean ± standard deviation (SD) for continuous and frequency (percentage) for categorical variables. The ANOVA, t-test, and chi-square test were used to compare variables between study groups in the simple analysis step. A multiple logistic regression analysis was done between all pollutants criteria as independent variables with breast density as a dichotomous dependent variable (low = 0 and high =1). This analysis was done via two non-stepwise and stepwise algorithms and the result of the stepwise algorithm was chosen as significant pollution criteria. After that, another logistic regression analysis was done to evaluate whether the effects of pollutants on breast density were independent or affected by potential confounding variables. This analysis was done as three models. For the first one, only significant pollutants were considered in the model. In the second model, medical and demographic variables were considered in addition to pollutants. In the last model, the history of medicine and supplement use was added to the previous variables. In the logistic regression analysis, odds ratio (OR) with 95% confidence interval (CI) was reported in addition to the p-value. All calculations were performed in IBM SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp) and the charts were drawn with MS Excel (Microsoft Co., Redmond, WA, USA). P-value < 0.05 was considered significant.

**Results**

Based on inclusion criteria 813 women were screened in this study. We excluded participants who were suspicious for malignancy in the current mammography (n=14), and who had written an incomplete address (n=8); finally 791 eligible women were recruited.

The mean age was 50.14 ± 7.61 (38-80) years old. About half of the women (50.1%) were premenopausal, and half of them were menopause (49.9%) at time of recruitment in the study. In the mammographies, low breast density was reported in 34.8% (n = 299) and high breast density in 62.2% (n = 492). Table 1 compares general and reproductive factors and other variables between breast density categories. As shown, all variables except the age of menarche and the whole breastfeeding duration had a statistically significant difference between two groups of breast density (P-value <0.05). The comparison between the 4 categories of MBD is presented in supplementary table 1.
| Variables                        | Low density | High density | P-value |
|---------------------------------|-------------|--------------|---------|
| **Age (years)**                 | 53.25 ± 8.29 | 48.25 ± 6.47 | <0.001  |
| **Body mass index (Kg/m^2)**   | 29.80 ± 5.35 | 27.19 ± 4.16 | <0.001  |
| **Age of menarche (years)**    | 13.69 ±1.57  | 13.51 ± 1.49 | 0.359   |
| **Age at first birth (years)** | 21.32 ± 5.22 | 22.46 ± 5.32 | 0.006   |
| **Parity (count)**             | 2.59 ± 1.58  | 1.96 ± 1.30  | <0.001  |
| **Breastfeeding duration (months)** | 35.14 ± 32.48 | 32.76 ± 29.30 | 0.290   |
| **Menopause**                   |             |              |         |
| No                              | 93 (23.5%)  | 303 (76.5%)  | <0.001  |
| Yes                             | 206 (52.2%) | 189 (47.8%)  |         |
| **History of OCP**             |             |              |         |
| No                              | 160 (32.6%) | 331 (67.4%)  | <0.001  |
| Yes                             | 139 (46.3%) | 161 (53.7%)  |         |
| **Smoking**                     |             |              |         |
| No                              | 261 (36.5%) | 455 (63.5%)  | 0.016   |
| Active or passive               | 38 (50.7%)  | 37 (49.3%)   |         |
| **Occupation**                  |             |              |         |
| Housewife                       | 264 (39.3%) | 407 (60.7%)  | 0.008   |
| Employed                        | 20 (23%)    | 67 (77%)     |         |
| Retired                         | 15 (45.5%)  | 18 (54.5%)   |         |
| **Metformin**                   |             |              |         |
| No                              | 250 (35.7%) | 450 (64.3%)  | 0.001   |
| Yes                             | 49 (53.8%)  | 42 (46.2%)   |         |
| **Aspirin**                     |             |              |         |
| No                              | 239 (34.9%) | 446 (65.1%)  | <0.001  |
| Yes                             | 60 (56.6%)  | 46 (43.4%)   |         |
| **Calcium**                     |             |              |         |
| No                              | 143 (32.5%) | 297 (67.5%)  | 0.001   |
| Yes                             | 156 (44.4%) | 195 (55.6%)  |         |
| **Vitamin D**                   |             |              |         |
| No                              | 164 (41.2%) | 234 (58.8%)  | 0.047   |
| Yes                             | 135 (34.4%) | 258 (65.6%)  |         |
| **Vitamin E**                   |             |              |         |
| No                              | 247 (38.3%) | 398 (61.7%)  | 0.547   |
| Yes                             | 52 (35.6%)  | 94 (64.4%)   |         |

Percent present between categories of each variable. P-values were computed with t-test for continuous and chi-square test for categorical variables.
| Variables                  | Low density | High density | P-value |
|---------------------------|-------------|--------------|---------|
| **Evening Primrose oil**  |             |              |         |
| No                        | 287 (38.2%) | 465 (61.8%)  | 0.353   |
| Yes                       | 12 (30.8%)  | 27 (69.2%)   |         |
| **Omega-3**               |             |              |         |
| No                        | 264 (37.9%) | 432 (62.1%)  | 0.896   |
| Yes                       | 35 (37.2%)  | 59 (62.8%)   |         |
| **History of Breast Disease** |             |              |         |
| No                        | 217 (35.6%) | 392 (64.4%)  | 0.021   |
| Yes                       | 82 (45.1%)  | 100 (54.9%)  |         |

Percent present between categories of each variable. P-values were computed with t-test for continuous and chi-square test for categorical variables.

In the first step, in a univariate analysis using a t-test, all six pollutants criteria were compared between low and high breast density. In this comparison, except for ambient air CO, which was on the borderline statistically significant (P-value = 0.054), other variables were not significantly different between the two groups (Figure 1 & Supplementary table 2). Due to an unclear trend of ambient criteria air pollutants between the four categories of MBD, the comparison has been conducted only between high and low breast densities; and the comparison between the 4 categories is presented in the supplementary table 3.

Unlike univariate analysis, multiple regression analysis between six ambient air pollutants and MBD showed that outdoor air NO₂ (P-value = 0.003) and CO (P-value = 0.001) had a significant relationship with breast density. Logistic regression analysis with stepwise algorithm and breast density as a dependent variable showed that an increase in each unit of NO₂ (ppb) exposure was associated with an increased risk of breast density with an OR equal to 1.04 (95% CI: 1.01 to 1.07); and an OR equal to 1.47 for each 10 unit increase in NO₂. Furthermore, CO level was associated with a decreasing risk of breast density in each 1 ppm (OR = 0.33, 95% CI = 0.17 to 0.64). None of the other pollutants were associated with breast density (Table 2).
Table 2
Stepwise and Non-stepwise logistic regression for criteria air pollutants with possible impact on mammographic breast density

|                  | Non-stepwise algorithm |                       |                       | Stepwise algorithm |                       |                       |
|------------------|------------------------|-----------------------|-----------------------|--------------------|-----------------------|-----------------------|
|                  | P-value | OR   | 95% C.I Lower | 95% C.I Upper | P-value | OR   | 95% C.I Lower | 95% C.I Upper |
| CO (ppm)         | 0.024   | 0.429 | 0.206        | 0.893        | 0.001   | 0.331 | 0.172        | 0.637        |
| NO2 (ppb)        | 0.055   | 1.045 | 0.999        | 1.093        | 0.003   | 1.039 | 1.013        | 1.066        |
| O3 (ppb)         | 0.870   | 0.988 | 0.852        | 1.145        |         |       |             |              |
| SO2 (ppb)        | 0.605   | 0.926 | 0.692        | 1.240        |         |       |             |              |
| PM10 (µg/m³)     | 0.378   | 0.944 | 0.829        | 1.073        |         |       |             |              |
| PM2.5 (µg/m³)    | 0.305   | 1.129 | 0.896        | 1.422        |         |       |             |              |
| Constant         | 0.000   | 1.754 | --           | --           | 0.000   | 1.758 | --           | --           |

OR = Odds ratio, C.I = Confidence interval, NO2 = Nitrogen dioxide (NO₂), SO2 = Sulfur dioxide, CO = Carbon monoxide, O₃ = Ozone, PM = Particulate matter.

In order to evaluate whether the effects of pollutants on MBD is independent or disappears under the influences of confounding variables, two others multiple analyses were performed. In the first model, basic and reproductive factors (age, body mass index (BMI), Smoking, history of OCP usage, parity, menopause, and history of breast disease) were entered into the model. In the second model, metformin and aspirin intake, vitamin D, and calcium consumption were also entered into the model. Table 3 illustrates the results of the three models. Finally, multiple logistic regression analysis showed that ambient air CO (P = 0.018) and NO₂ (P = 0.022) had independent effects on the breast density.
Table 3
Three multiple logistic regression models for the effect of ambient air pollutants on mammographic breast density considering confounder variables

|                | P-value | OR   | 95% C.I. for OR |
|----------------|---------|------|----------------|
|                |         |      | Lower    | Upper   |
| Model 1        |         |      |          |         |
| CO             | 0.001   | 0.331| 0.172    | 0.637   |
| NO2            | 0.003   | 1.039| 1.013    | 1.066   |
| Constant       | <0.001  | 1.758|          |         |
| Model 2        |         |      |          |         |
| CO             | 0.020   | 0.411| 0.195    | 0.868   |
| NO2            | 0.026   | 1.034| 1.004    | 1.064   |
| Age            | 0.000   | 0.942| 0.915    | 0.971   |
| BMI            | 0.000   | 0.884| 0.851    | 0.919   |
| Smoking        | 0.063   | 0.602| 0.353    | 1.029   |
| History of OCP | 0.000   | 0.526| 0.375    | 0.738   |
| Menopause      | 0.002   | 0.522| 0.348    | 0.782   |
| Parity         | 0.708   | 0.975| 0.856    | 1.111   |
| History of Breast disease | 0.106 | 0.728| 0.495 | 1.070   |
| Constant       | <0.001  | 2454.3|          |         |
| Model 3        |         |      |          |         |
| CO             | 0.018   | 0.404| 0.190    | 0.856   |
| NO2            | 0.022   | 1.035| 1.005    | 1.066   |
| Age            | 0.000   | 0.947| 0.919    | 0.976   |
| BMI            | 0.000   | 0.884| 0.851    | 0.920   |
| Smoking        | 0.088   | 0.624| 0.363    | 1.072   |
| History of OCP | 0.000   | 0.536| 0.381    | 0.753   |
| Menopause      | 0.004   | 0.544| 0.360    | 0.823   |
| Parity         | 0.938   | 0.995| 0.872    | 1.135   |
| History of Breast disease | 0.124 | 0.735| 0.496 | 1.088   |
| Metformin      | 0.726   | 0.913| 0.547    | 1.524   |

OR = Odds ratio, C.I = Confidence interval, NO₂ = Nitrogen dioxide (NO₂), SO₂ = Sulfur dioxide, CO = Carbon monoxide, O₃ = Ozone, PM = Particulate matter.
In addition, a separate analysis was performed considering menopausal status. The relationship between ambient air \( \text{NO}_2 \) (OR = 1.07, 95% CI: 1.003-1.139, \( P \)-value = 0.041) and \( \text{CO} \) (OR = 0.34, 95% CI: 0.120-0.955, \( P \)-value = 0.041) with MBD was observed only in menopausal women in the same direction as stated. In premenopausal women, breast density was not associated with ambient air pollutants (Supplementary table 4).

The comparison in breast density in women who live a lifetime in Tehran and other women didn’t show any significant difference (data not shown in table).

**Discussion**

The present study has evaluated the precise impact of long-term exposure to six criteria ambient air pollutants on MBD in Iranian women for the first time. Actually, many known and unknown factors are involved in breast tissue changes and eventually in breast cancer and it’s not possible to control all confounding factors in a single context. By the way, based on the available evidence, we tried to evaluate the effects of six criteria ambient air pollutants on breast density considering the factors that seem to have an impact on MBD (basic and reproductive factors, aspirin, metformin, and supplement intake). To the best of our knowledge, there is no study with this broad level of assessment.

Our results represented that outdoor air \( \text{NO}_2 \) and \( \text{CO} \) exposure had statistically significant impacts on MBD. We found that an increased level of \( \text{NO}_2 \), as a marker of traffic-related air pollution (27), is associated with a higher MBD. Furthermore, ambient air \( \text{CO} \) concentration was associated with a lower MBD, while other criteria air pollutants were not related to MBD.

Our present results about ambient air \( \text{NO}_2 \) and PMx (PM\(_{2.5}\) & PM\(_{10}\)) concentration were consistent with a recent systematic study and meta-analysis that found an increased risk of breast cancer with an increase in each 10 unit in \( \text{NO}_2 \) exposure (Hazard ratio (HR) = 1.02, 95% CI = 1.01-1.04), while PM\(_{2.5}\) and PM\(_{10}\) revealed no statistically significant associations with breast cancer risk (11). The results of our study on the relationship between air pollutants and MBD seem to be in line with studies that have examined the relationship between these pollutants and breast cancer.
Limited studies have evaluated the association between criteria ambient air pollutants and MBD with inconsistent results (16, 17, 19). Similar to our study, Du Pre and their colleague's results in the Nurses' Health Study couldn't support that recent particulate matter (PM$_{2.5}$, PM air$_{2.5-10}$, PM$_{10}$) or roadway exposure influenced breast density (16). Two other studies had contradictory results with the present study (17, 19). The Danish Diet, Cancer and Health Cohort investigated the association between long-term exposure to traffic-related air pollution (NO$_2$, NO$_x$) and MBD in a prospective cohort of women aged 50 and older. They found a reverse association between air NO$_2$ level and MBD (OR= 0.89, 95% CI: 0.80-0.89 per 10 µg/m$^3$) with no interaction with menopause, smoking, or obesity (17). In Yaghjyan et al. study, women higher than 40 years old with known residential zip codes and estimated PM$_{2.5}$ and O$_3$ levels for the year preceding the mammogram date were included. They found that women with extreme breast density had higher mean PM$_{2.5}$ and lower O$_3$ exposure levels (19).

Numerous studies in line with our study have investigated the relationship between endocrine-disrupting chemicals (EDCs) and heavy metals with MBD (13, 14, 18). In a cross-sectional study in 725 women (40-65 years old), a higher urinary level of magnesium was associated with a higher MBD (13). In postmenopausal women (n = 264), women with high serum levels of BPA and mono-ethyl phthalate had an elevated breast density (14). In a large-scale study (n= 222,581), the relation of the MBD of women who underwent a routine screening mammogram in 2011 and residential levels of ambient air polycyclic aromatic hydrocarbons (PAHs) and metals was assessed. Higher residential levels of arsenic, cobalt, lead, manganese, nickel, or PAHs were individually associated with breast density. Comparing the highest to the lowest quartile, higher odds for dense breasts were observed for cobalt (OR = 1.60, 95% CI 1.56–1.64) and lead (OR = 1.56, 95% CI 1.52–1.64). These associations were stronger in premenopausal women (18). An exception is one cross-sectional study of PCBs, which reported some PCB congeners’ plasma levels were associated with lower MBD in postmenopausal women (15).

Consistent with the present study, a review study by White and colleagues that summarized eight case-control studies and nine cohort studies suggested little evidence to support an association between particulate matter and breast cancer risk. More consistent findings have reported a relation between NO$_2$ or NO$_x$ level and breast cancer (28).

In this study, we found a reverse association between CO level and MBD. Two recent studies that evaluated the effect of ambient air CO on breast cancer had equivocal results. A Korean study reported that CO concentration was positively and significantly associated with breast cancer (OR= 1.08, 95% CI= 1.06-1.10) (29) and another cohort study in Taiwan found that women who had CO poisoning were at a lower risk of developing breast cancer (30). We did not find any studies that examined the association between MBD and carbon monoxide. Since there is a positive correlation between MBD and breast cancer, the results of our study are consistent with the Taiwanese study.

It is very important to note that according to the evidence, environmental pollutants are associated with a higher risk of invasive breast cancer and increased mortality in these patients. Investigation on breast
cancer cases has reported that PM$_{2.5}$ and NO$_2$ were associated with breast cancer (HR = 1.05; 95% CI: 0.99-1.11) and (HR = 1.06; 95% CI: 1.02-1.11), respectively. Invasive breast cancer was associated with PM$_{2.5}$ only in the Western United States (HR=1.14; 95% CI: 1.02-1.27) and NO$_2$ only in the Southern United States (HR=1.16; 95% CI:1.01-1.33) (31). The meta-analysis showed that each 10 µg/m$^3$ of PM$_{2.5}$ was associated with a 1.17 (95% CI: 1.05-1.30) fold risk of BC mortality, and each 10 µg/m$^3$ of PM$_{10}$ was associated with a 1.11 (95% CI: 1.02-1.21) fold risk of BC mortality. However, neither PM$_{10}$ nor PM$_{2.5}$ was found to be significantly associated with BC morbidity (32). These findings show the importance of research on the impact of pollutants on women's health, and public health professionals and policymakers should consider these characteristics to develop relevant interventions and prevention strategies that are more cost-effective and efficient.

The advantage of this study is, we considered all the possibly effective factors and known determinants of MBD, all of which are estrogen-related.

As it was demonstrated in Table 1, 91 (11.5%) and 106 (13.4%) women in the present study sample consumed metformin and aspirin, respectively. Numerous studies have evaluated the effects of aspirin and metformin on MBD with inconsistent results (33–36). In addition some researches have shown that higher vitamin D and calcium intake are associated with decreased MBD (37–39).

According to the findings of the mentioned studies and the high percentage of women who had taken metformin (11.5%), aspirin (13.4%), vitamin D (49.7%), and calcium (44.4%) in our study, it seems that without considering the use of these drugs, the results may not be expressed correctly. However, our findings showed that even by considering these factors, the results did not change.

It should be noted that most of the sampling in this study coincided with the worldwide onset of COVID-19 pandemic. Therefore, it is possible that the participants during this period were women at higher risk of breast cancer who had been referred for screening despite the COVID-19 pandemic.

**Conclusion**

In conclusion, based on our results, MBD was associated with higher levels of ambient air NO$_2$ and lower levels of CO. Considering our results and other evidences, important decisions at the national level are essential to reduce environmental pollution, especially air, to achieve sustainable development. Perhaps MBD monitoring as an available tool in each population, can help the prediction of future breast cancer occurrence and finding the high-risk geographic areas.

**List Of Abbreviations**

MBD: Mammographic breast density; IARC: International Agency for Research on Cancer; BPA: Bisphenol-A; PCBs: Polychlorinated biphenyl; NO$_2$: Nitrogen dioxide; SO$_2$: Sulfur dioxide; CO: Carbon monoxide; O$_3$: Ozone; PM: Particulate matter; OCP: Oral contraceptive; ACR: American College of Radiology; BI-RADS:
Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1398.897), and all participants have signed an informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available on reasonable request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was funded by Institute for Environmental Research (IER) and by an academic research grant from the Deputy of Research of Tehran University of Medical Sciences (grant number: 98-3-259-45184)

Authors’ contributions

BE contributed to the conception, design of the work, interpretation of data, and drafting of the manuscript. SA, RO, MSH contributed to the design of the work and substantively revised the manuscript. MMN contributed to the analysis and interpretation of data. KN, AA, MA, and LB contributed to the conception and acquisition of the data. MSH as a corresponding author contributed in all steps. All authors read and approved the final manuscript. They accepted their own contribution to this manuscript and accepted all responsibilities.

Acknowledgement

The authors are grateful to Tehran Air Quality Control Company (TAQCC) for providing ambient air pollutants concentrations data. Also, the authors would like to thank Zohre Samadi, Mina Mahmoodi, and Afsaneh Teimoori, for their assistance in collecting data, which made this project possible. We would like to express our special thanks to Faezeh Izadpanah who helped us in extracting environmental data.
References

1. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncology. 2013;14(13):1262.

2. Morishita M, Adar SD, D'Souza J, Ziemia RA, Bard RL, Spino C, et al. Effect of portable air filtration systems on personal exposure to fine particulate matter and blood pressure among residents in a low-income senior facility: a randomized clinical trial. JAMA internal medicine. 2018;178(10):1350–7.

3. Faridi S, Shamsipour M, Krzyzanowski M, Künzli N, Amini H, Azimi F, et al. Long-term trends and health impact of PM2.5 and O3 in Tehran, Iran, 2006–2015. Environ Int. 2018;114:37–49.

4. Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72(17):2054–70.

5. Yu W, Guo Y, Shi L, Li S. The association between long-term exposure to low-level PM2.5 and mortality in the state of Queensland, Australia: A modelling study with the difference-in-differences approach. PLoS Med. 2020;17(6):e1003141.

6. Huang J, Chan PS, Lok V, Chen X, Ding H, Jin Y, et al. Global incidence and mortality of breast cancer: a trend analysis. Aging. 2021;13(4):5748.

7. Perry N, Allgood P, Milner S, Mokbel K, Duffy S. Mammographic breast density by area of residence: possible evidence of higher density in urban areas. Curr Med Res Opin. 2008;24(2):365–8.

8. Wei Y, Davis J, Bina WF. Ambient air pollution is associated with the increased incidence of breast cancer in US. Int J Environ Health Res. 2012;22(1):12–21.

9. Ammons S, Aja H, Ghazarian AA, Lai GY, Ellison GL. Perception of Worry of Harm from Air Pollution. Results from the Health Information National Trends Survey (HINTS); 2021.

10. Hill P, Wynder EL. Nicotine and cotinine in breast fluid. Cancer letters. 1979;6(4-5):251–4.

11. Wei W, Wu B-J, Wu Y, Tong Z-T, Zhong F, Hu C-Y. Association between long-term ambient air pollution exposure and the risk of breast cancer: a systematic review and meta-analysis. Environmental Science and Pollution Research. 2021:1–19.

12. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res. 2011;13(6):1–12.

13. Mora-Pinzon MC, Trentham-Dietz A, Gangnon RE, Adams SV, Hampton JM, Burnside E, et al. Urinary magnesium and other elements in relation to mammographic Breast density, a measure of breast cancer risk. Nutrition cancer. 2018;70(3):441–6.

14. Sprague BL, Trentham-Dietz A, Hedman CJ, Wang J, Hemming JD, Hampton JM, et al. Circulating serum xenoestrogens and mammographic breast density. Breast Cancer Res. 2013;15(3):1–8.

15. Diaorio C, Dumas I, Sandanger TM, Ayotte P. Levels of circulating polychlorinated biphenyls and mammographic breast density. Anticancer research. 2013;33(12):5483–9.

16. DuPre NC, Hart JE, Bertrant KA, Kraft P, Laden F, Tamimi RM. Residential particulate matter and distance to roadways in relation to mammographic density: results from the Nurses’ Health Studies.
Breast Cancer Res. 2017;19(1):1–10.

17. Huynh S, von Euler-Chelpin M, Raaschou-Nielsen O, Hertel O, Tjønneland A, Lynge E, et al. Long-term exposure to air pollution and mammographic density in the Danish Diet, Cancer and Health cohort. Environ Health. 2015;14(1):1–7.

18. White AJ, Weinberg CR, O’Meara ES, Sandler DP, Sprague BL. Airborne metals and polycyclic aromatic hydrocarbons in relation to mammographic breast density. Breast Cancer Res. 2019;21(1):1–12.

19. Yaghjyan L, Arao R, Brokamp C, O’Meara ES, Sprague BL, Ghita G, et al. Association between air pollution and mammographic breast density in the Breast Cancer Surveillance Consortium. Breast Cancer Res. 2017;19(1):1–10.

20. Faridi S, Niazi S, Yousefian F, Azimi F, Pasalari H, Momeniha F, et al. Spatial homogeneity and heterogeneity of ambient air pollutants in Tehran. Science of The Total Environment. 2019;697:134123.

21. Sickles E, d’Orsi C, Bassett L, Appleton C, Berg W, Burnside E. Acr bi-rads® mammography. ACR BI-RADS® atlas, breast imaging reporting and data system. 2013;5:2013.

22. UNION P. Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe. Official Journal of the European Union. 2008.

23. Barrero M, Orza J, Cabello M, Cantón L. Categorisation of air quality monitoring stations by evaluation of PM10 variability. Science of The Total Environment. 2015;524:225–36.

24. USEPA. QA Handbook for Air Pollution Measurement Systems Volume II Ambient Air Quality Monitoring Program2013.

25. Song C, He J, Wu L, Jin T, Chen X, Li R, et al. Health burden attributable to ambient PM2. 5 in China. Environmental pollution. 2017;223:575–86.

26. Jafari AJ, Faridi S, Momeniha F. Temporal variations of atmospheric benzene and its health effects in Tehran megacity (2010-2013). Environ Sci Pollut Res. 2019;26(17):17214–23.

27. Beckettman B, Jerrett M, Brook JR, Verma DK, Arain MA, Finkelstein MM. Correlation of nitrogen dioxide with other traffic pollutants near a major expressway. Atmos Environ. 2008;42(2):275–90.

28. White AJ, Bradshaw PT, Hamra GB. Air pollution and breast cancer: a review. Current epidemiology reports. 2018;5(2):92–100.

29. Hwang J, Bae H, Choi S, Yi H, Ko B, Kim N. Impact of air pollution on breast cancer incidence and mortality: a nationwide analysis in South Korea. Scientific reports. 2020;10(1):1–7.

30. Huang C-C, Ho C-H, Chen Y-C, Hsu C-C, Lin H-J, Tian Y-F, et al. Impact of carbon monoxide poisoning on the risk of breast cancer. Scientific reports. 2020;10(1):1–8.

31. White AJ, Keller JP, Zhao S, Carroll R, Kaufman JD, Sandler DP. Air pollution, clustering of particulate matter components, and breast cancer in the sister study: a US-wide cohort. Environmental health perspectives. 2019;127(10):107002.
32. Zhang Z, Yan W, Chen Q, Zhou N, Xu Y. The relationship between exposure to particulate matter and breast cancer incidence and mortality: a meta-analysis. Medicine. 2019;98(50).

33. Wood ME, Sprague BL, Oustimov A, Synnstvedt MB, Cuke M, Conant EF, et al. Aspirin use is associated with lower mammographic density in a large screening cohort. Breast cancer research treatment. 2017;162(3):419–25.

34. Yaghjyan L, Wijayabahu A, Eliassen AH, Colditz G, Rosner B, Tamimi RM. Associations of aspirin and other anti-inflammatory medications with mammographic breast density and breast cancer risk. Cancer Causes Control. 2020;31:827–37.

35. Buschard K, Thomassen K, Lynge E, Vejborg I, Tjønneland A, von Euler-Chelpin M, et al. Diabetes, diabetes treatment, and mammographic density in Danish Diet, Cancer, and Health cohort. Cancer Causes Control. 2017;28(1):13–21.

36. Oskar S, Engmann NJ, Azus AR, Tehranifar P. Gestational diabetes, type II diabetes, and mammographic breast density in a US racially diverse population screened for breast cancer. Cancer Causes Control. 2018;29(8):731–6.

37. Fair AM, Lewis TJ, Sanderson M, Dupont WD, Fletcher S, Egan KM, et al. Increased vitamin D and calcium intake associated with reduced mammographic breast density among premenopausal women. Nutr Res. 2015;35(10):851–7.

38. Brisson J, Bérubé S, Diorio C, Mâsse B, Lemieux J, Duchesne T, et al. A randomized double-blind placebo-controlled trial of the effect of vitamin D3 supplementation on breast density in premenopausal women. Cancer Epidemiology Prevention Biomarkers. 2017;26(8):1233–41.

39. Alipour S, Shirzad N, Sepidarkish M, Saberi A, Bayani L, Hosseini L. The Effect of Vitamin D Supplementation on Breast Density Changes: A Clinical Trial Study. Nutrition cancer. 2018;70(3):425–30.

Figures
Figure 1

Comparison of participants' exposure to ambient air pollutants with high and low mammographic breast density. The P-values of the t-tests were P-value = 0.054 (CO), P-value = 0.404 (O3), P-value = 0.601 (NO2), P-value = 0.125 (SO2), P-value = 0.233 (PM10), P-value = 0.295 (PM2.5). Further information is presented in supplementary table 2.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTablesFinal.docx