Associations between NO2, PM2.5, Proximity to greenness and incident breast cancer

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Breast cancer

- In Canada in 2017,
  - 26,300 women newly diagnosed cases
  - 5,000 women deaths
- Most diagnoses postmenopausal
- Premenopausal cancers generally more aggressive
- Differing etiology by menopausal status
Air Pollution and Breast Cancer: Pathways

- Air Pollution is recognized as a human carcinogen.
- Experimental data provide some evidence supporting a link between ambient air pollution and breast cancer
  - PAHs which can cause oxidative stress and mammary tumors in laboratory animals
  - Benzene, present in traffic exhaust, has been linked to mammary tumors in mice
  - PM showed DNA-damaging activity and estrogenicity in human breast cancer cells
Greenness and Health: Pathways

- Healthy Lifestyles
  - Restoration from stress
  - Increased opportunity for physical activities
  - Especially important for some (e.g., elderly, mothers with infants, children, those with disabilities)
  - Enhancing Social networks

- Environmental impacts
  - Absorb air pollution
  - Provide cooling
  - Shelter from UV
  - Reducing noise

- Multiple pathways could be involved
Greenness and Breast Cancer?

- Green spaces have been positively associated with increased levels of physical activity.
- Physical activity has been associated with reduced risk of breast cancer in some studies.
- Green areas tend to have lower levels of air pollution.
- Most of these mechanisms however, may be relevant for green spaces such as parks or forests.
- Agricultural areas has been associated with increased risks of cancer.
- Self-selection bias?
Previous studies Greenness and Breast Cancer

- Inverse association noted within US Nurses Health Study
  - 13% lower mortality among those in upper quintile relative to lowest (James et al, 2018)

- Inverse associations noted in multi-site case-control study in Spain (O'Callaghan-Gordo C et al, 2018)

Table 3

<table>
<thead>
<tr>
<th>Presence of urban green area at 300 m buffer</th>
<th>Densely populated areas, 2423 (88%)</th>
<th>Less than densely populated areas, 325 (12%)</th>
<th>n (%)/median (IQR)</th>
<th>OR (95% CI) ±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of agricultural area at 300 m buffer</td>
<td>Densely populated areas, 2423 (88%)</td>
<td>Less than densely populated areas, 325 (12%)</td>
<td>n (%)/median (IQR)</td>
<td>OR (95% CI) ±</td>
</tr>
<tr>
<td>No</td>
<td>321 (17)</td>
<td>1.00 (ref)</td>
<td>4 (4)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>1545 (83)</td>
<td>0.66 (0.5–0.88)</td>
<td>93 (96)</td>
<td>0.22 (0.02–2.7)</td>
</tr>
<tr>
<td>Presence of agricultural area at 300 m buffer</td>
<td>2099 (87)</td>
<td>1.00 (ref)</td>
<td>66 (20)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>No</td>
<td>324 (13)</td>
<td>1.65 (1.27–2.14)</td>
<td>259 (80)</td>
<td>0.72 (0.37–1.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.21 (0.11)</td>
<td>1.36 (1.19–1.56)</td>
<td>0.34 (0.16)</td>
<td>0.96 (0.72–1.29)</td>
</tr>
</tbody>
</table>

IQR: Interquartile range; ± Model adjusted for adjusted for age, education, individual socioeconomic status (low, middle, high), area level socioeconomic status (quintiles) and number of children (0 versus ≥1); Increase is per 1 IQR based on the NDVI on all the study population in 300 m buffer.
Canadian National Breast Screening Study

- **Study Design:** Prospective randomized controlled trial
  - Screening
  - Usual care group

- **Sample Size:** Approximately 89,000 women, aged 40-59 y

- **Enrollment period:** 1980 -1985

- **Outcome ascertainment:** Probabilistic record linkage to Canadian Mortality Database, and Canadian Cancer Registry (through 2005)

- 6,503 incident breast cancers during ~ 2 decades follow-up
Risk Factor data collected

- From baseline questionnaires
- Anthropometric measures from Nurses
- Risk Factors included
  - BMI
  - Family history of breast cancer
  - Oral contraceptive, and hormone replacement therapy
  - Smoking Status
  - Reproductive history
  - Breast self-examination practices
  - SES (marital status, education, etc)
  - Ethnicity
Residential Information

- Six character postal code at baseline
- Complete information as required for follow-up
- Information if they moved during 6 year active follow-up
PM2.5 data

- Remote sensing
- At resolution of 10 km x 10 km
- Correlates well with fixed site monitors (r ~0.76)
- Mean 9.50 µg/m³
  - 25th P: 6.40
  - 75th P: 12.40
Assignment of Air Pollution: NO$_2$

- Based on a National LUR developed by Hystad et al (2006)

- First stage
  - For each fixed site monitoring station, derived satellite-based estimates, and geographical variables
  - Stepwise regression to identify LUR models

- Second stage
  - Identify factors to capture local-scale gradients (i.e., highways, gas stations, major roads)
  - Identified concentrations near these selected sources in relation to background
  - Developed deterministic distance decay rates

- Model $R^2=0.73$
Assignment of Greenness

- Normal Difference Vegetation Index (NDVI)
- Used since 1973;
- Detect live green plant canopies in multispectral remote sensing data
- Derived from Landsat Thematic Mapper (1989 – 1997)
- Spatial Resolution of 30 m
- NDVI value: -1 (less green) to +1 (more green)
- Exposure assigned to residence at inception
- Assigned to centroid of 6 character postal codes
Statistical Analyses

- Descriptive statistics & correlations
- Cox Proportional Hazards Model
  - Hazard Ratios and 95% CI
  - Adjusted for
    - Individual risk factors
    - Contextual risk factors
- Menopausal status
  - Baseline information
  - Attained age through follow-up (i.e., 50, 52, 54)
- Effect modification by
  - Mobility status
  - Obesity
PM2.5 - Key Findings

Table 4

<table>
<thead>
<tr>
<th>Age at Menopause (years)</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast Cancers</td>
<td>HR[^a]</td>
</tr>
<tr>
<td>50</td>
<td>467</td>
<td>1.34</td>
</tr>
<tr>
<td>52</td>
<td>646</td>
<td>1.37</td>
</tr>
<tr>
<td>54</td>
<td>855</td>
<td>1.27</td>
</tr>
</tbody>
</table>

\[^a\]PM\(_{2.5}\) concentrations were assigned to participants' place of residence at baseline based on remote-sensing data collected between 1998 and 2006.

\[^b\]Using model IV, which included age, occupation, marital status, attained education, ever pregnant, Breast self examination (BSE), oral contraceptive (OC) use, Hormone replacement therapy (HRT), family history of breast cancer (BC) and age at menarche.
### Adjusted Rate Ratios, NO₂ and breast cancer (Goldberg et al, 2019 [under review])

<table>
<thead>
<tr>
<th>Regression model</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age cut-off, 50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model I</td>
<td>1.13</td>
<td>0.98-1.30</td>
</tr>
<tr>
<td>Model II</td>
<td>1.15</td>
<td>0.99-1.33</td>
</tr>
<tr>
<td>Model III</td>
<td>1.15</td>
<td>0.99-1.33</td>
</tr>
<tr>
<td>Model IV</td>
<td>1.15</td>
<td>0.99-1.34</td>
</tr>
<tr>
<td>Model V</td>
<td>1.13</td>
<td>0.94-1.37</td>
</tr>
<tr>
<td>Model V + PM₂.₅</td>
<td>1.09</td>
<td>0.89-1.35</td>
</tr>
<tr>
<td>Study</td>
<td>No. of cases</td>
<td>Exposure methodology</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Montreal hospital-based c-c study¹⁶</td>
<td>383</td>
<td>Postmenopausal women Dense LUR assigned at time of interview</td>
</tr>
<tr>
<td>Montreal population-based c-c study²⁶</td>
<td>679</td>
<td>Dense LUR assigned at time of interview</td>
</tr>
<tr>
<td>8-province c-c study⁶</td>
<td>1,140</td>
<td>National LUR assigned at time of interview</td>
</tr>
<tr>
<td>Sister cohort (USA)³³</td>
<td>1,749</td>
<td>Spatial model using fixed-site monitors</td>
</tr>
<tr>
<td>Danish Nurses Cohort³⁴</td>
<td>1,145</td>
<td>Emissions/Dispersion model</td>
</tr>
<tr>
<td>ESCAPE cohort (Europe, 15 cities)⁸</td>
<td>3,612</td>
<td>LUR back extrapolated at time of entry</td>
</tr>
<tr>
<td>Present study (age cut-off of 52 years)</td>
<td>5,851</td>
<td>National LUR assigned at time of entry</td>
</tr>
<tr>
<td>8-province Canadian c-c study⁷</td>
<td>619</td>
<td>Premenopausal women National LUR assigned at time of interview</td>
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<tr>
<td>Present study (age cut-off of 52 years)</td>
<td>646</td>
<td>National LUR assigned at time of entry</td>
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Pearson Correlations

<table>
<thead>
<tr>
<th></th>
<th>PM2.5</th>
<th>Greenness</th>
<th>NO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM2.5</td>
<td>1.0</td>
<td>-0.14</td>
<td>0.56</td>
</tr>
<tr>
<td>Greenness</td>
<td>1.0</td>
<td></td>
<td>-0.55</td>
</tr>
<tr>
<td>NO2</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>
Adjusted Rate Ratios of Breast Cancer (*per IQR increase in greenness)
Limitations

- Greater measurement error for premenopausal breast cancer
- Passive follow-up after the first 6 years
- Given the length of the follow-up interval, many subjects likely would have moved. Under a classical error model
  - introduce non-differential exposure measurement error (i.e., underestimate the risks)
**Strengths**

- Relatively large cohort with a large number of cases of incident breast cancer
- Ability to ascertain outcomes through record linkage
- Assignment of exposure to virtually all participants regardless of whether they lived in rural or urban areas
- Availability of individual-level risk factors that allowed us to adjust for smoking behaviours and body mass index
- Adjustment for possible area-wide effects
Future work

- Examine sub-types of breast cancer (morphology and receptor status)

- Examples:
  - Montreal study found stronger associations between NO2 among women exposed before the age of 35 years and those with ER+/PR+ receptor status
  - Increased risks were found in Sister Study Cohort for cases with positive oestrogen receptor and positive progesterone receptor status

- Mediation analyses of physical activity, obesity, and built environment exposures

- Consideration of other greenness metrics

- Self-selection biases (i.e., mover study)
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- Dr. Teresa To, Hospital for Sick Children, Toronto
- Mr. Claus Wall, University of Toronto

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