

Associations between NO₂, PM_{2.5}, Proximity to greenness and incident breast cancer



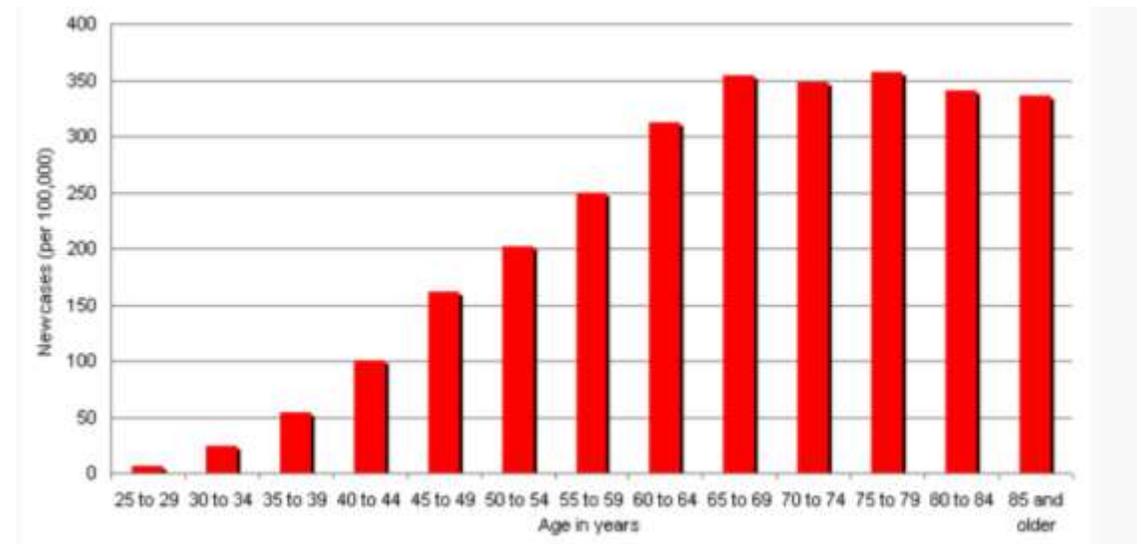
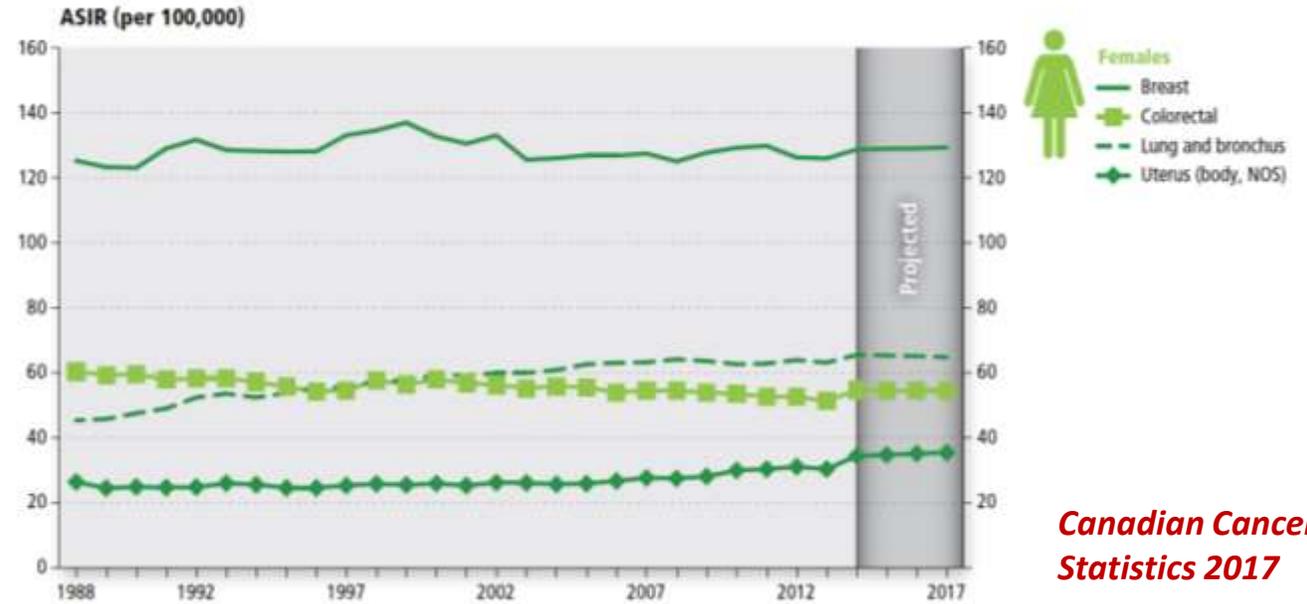
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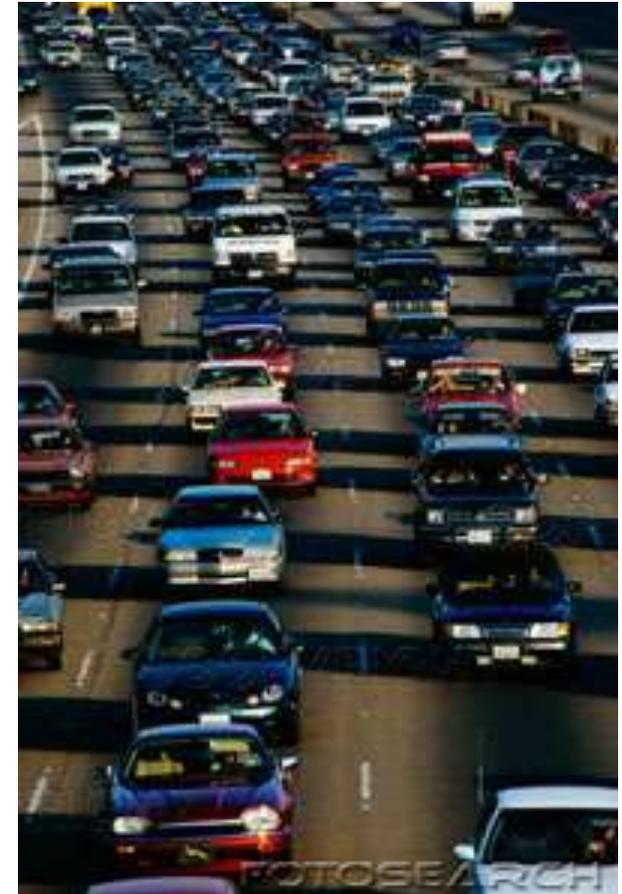
Breast cancer

- 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

Associations between presence of urban green areas, presence of agricultural areas, and surrounding greenness in 300 m buffer around the current residence and risk of breast cancer according to degree of urbanization.

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

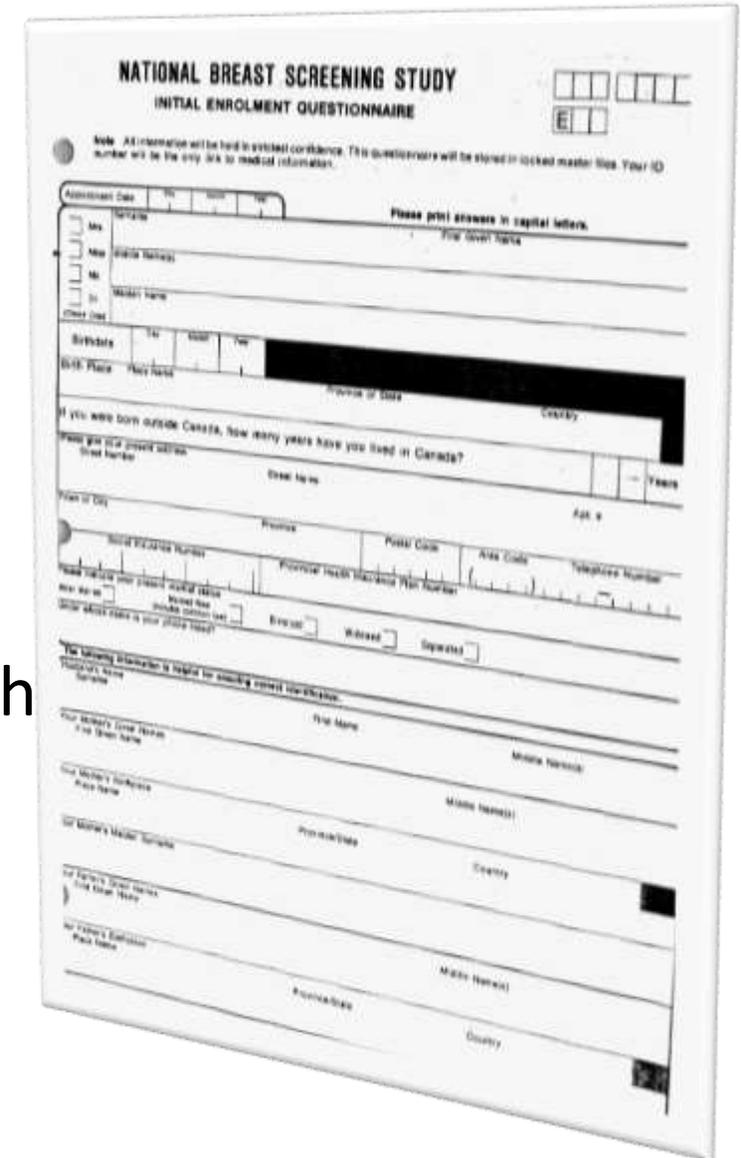
IQR: Interquartile range; [±] Model adjusted for adjusted for age, education, individual socioeconomic status (low, middle, high), area level socioeconomic status (quintiles) and number of children (0 versus ≥ 1); [#] Increase is per 1 IQR based on the NDVI on all the study population in 300 m buffer.

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

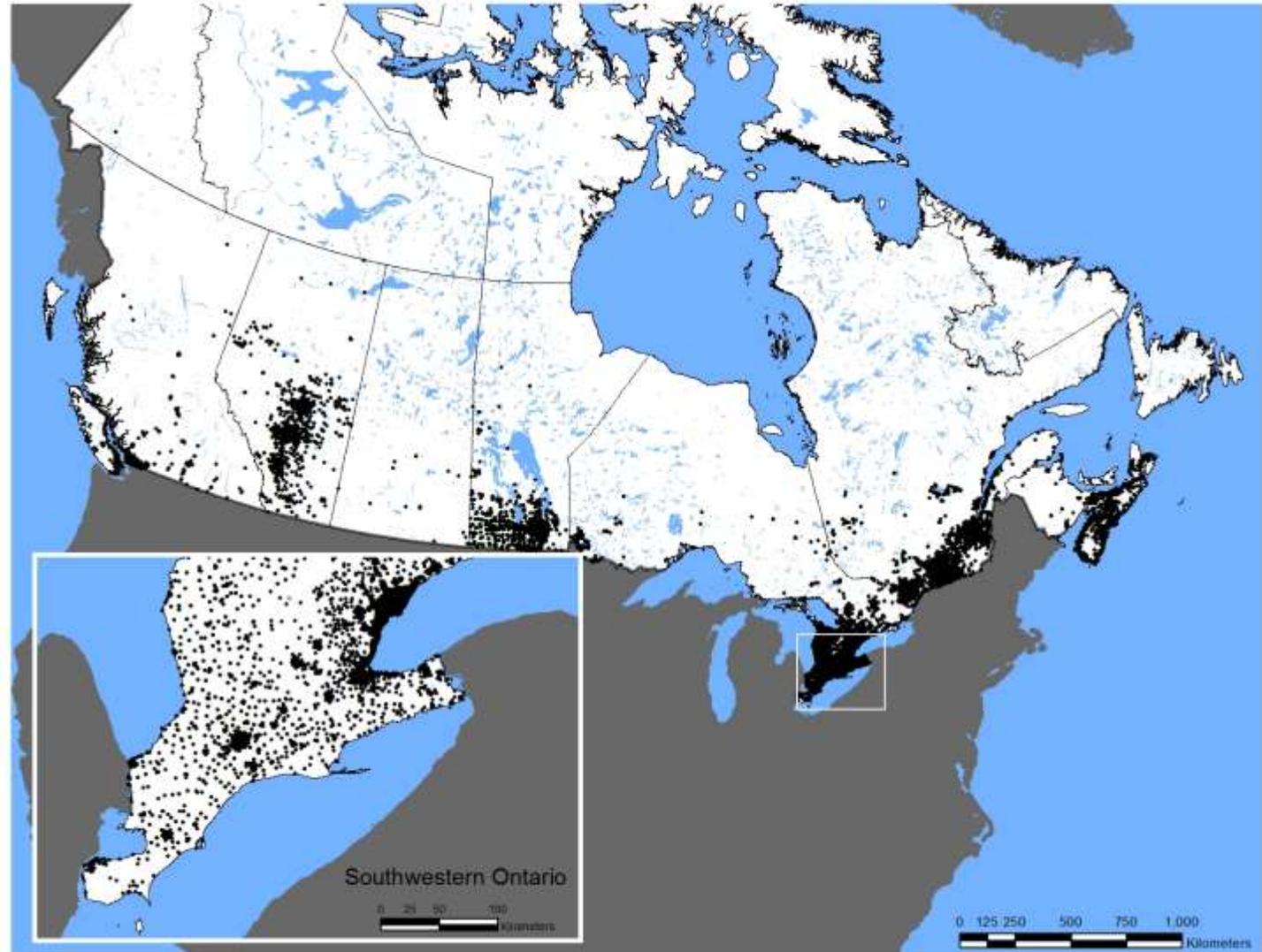
- From baseline questionnaires
- Anthropometric measures from Nurses
- Risk Factors included
 - BMI
 - Family history of breast cancer
 - Oral contraceptive, and hormone replacement therapy
 - Smoking Status
 - Reproductive history
 - Breast self-examination practices
 - SES (marital status, education,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



The image shows a form titled "NATIONAL BREAST SCREENING STUDY INITIAL ENROLMENT QUESTIONNAIRE". The form includes a header with the study name and a note: "All information will be held in strictest confidence. This questionnaire will be stored in locked master files. Your ID number will be the only link to medical information." Below the header, there are several sections for data entry, including: "Assessment Date", "Please print answers in capital letters", "Your given name", "Your family name", "Your date of birth", "Your sex", "Your province or state", "Your country", "If you were born outside Canada, how many years have you lived in Canada?", "How long your present address", "Your telephone number", "Your postal code", "Your area code", "Your telephone number", "Your health insurance plan number", "Your marital status", "Your education level", "Your occupation", "Your country of birth", "Your mother's given name", "Your mother's family name", "Your mother's date of birth", "Your mother's province or state", "Your mother's country", "Your father's given name", "Your father's family name", "Your father's date of birth", "Your father's province or state", "Your father's country".

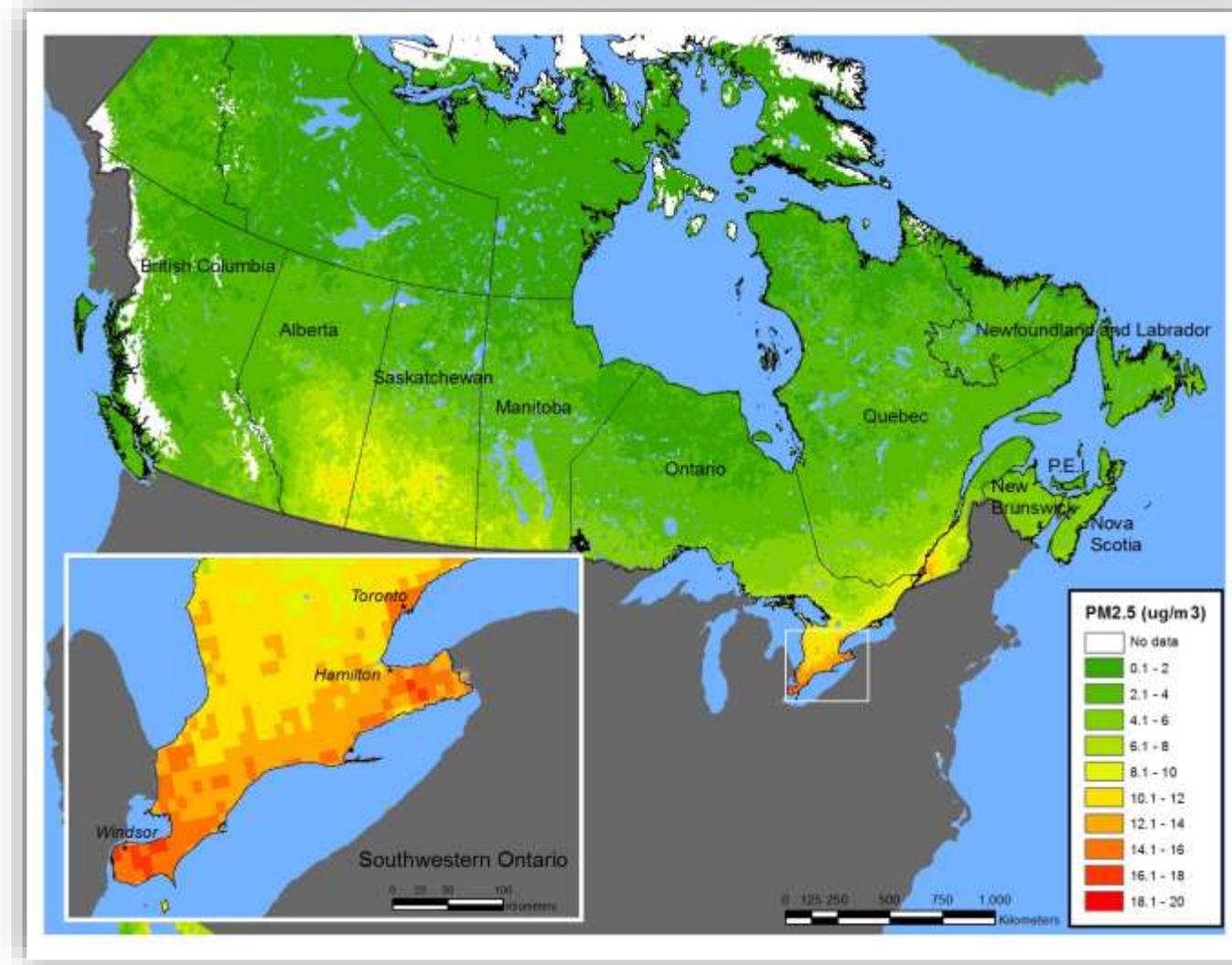
Residential Information

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



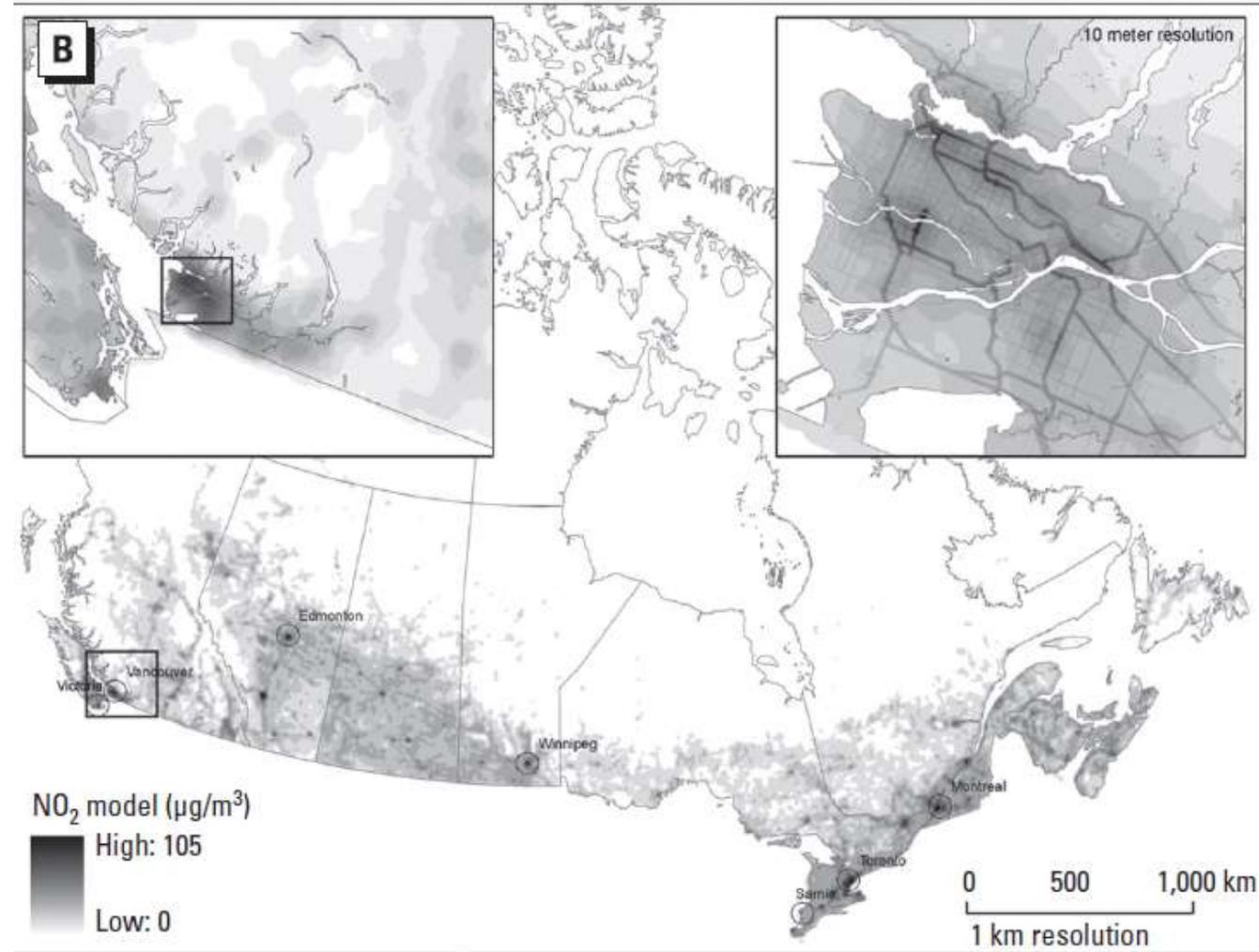
PM2.5 data

- Remote sensing
- Long term average (1998-2006)
- At resolution of 10 km x 10 km
- Correlates well with fixed site monitors ($r \sim 0.76$)
- Mean 9.50 $\mu\text{g}/\text{m}^3$
 - 25th P: 6.40
 - 75th P: 12.40



Assignment of Air Pollution: NO₂

- 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 R²=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

Adjusted hazard ratios (HRs) of incident breast cancer in relation to an increase of 10 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ ^a by varying definitions of age of menopause, Canadian National Breast Screening Study, 1982–2005

Age at Menopause (years)	Premenopausal			Postmenopausal		
	Breast Cancers	HR ^b	95% CI	Breast Cancers	HR	95% CI
50	467	1.34	1.02–1.76	5960	1.01	0.93–1.09
52	646	1.37	1.09–1.73	5781	0.99	0.92–1.06
54	855	1.27	1.04–1.55	5572	0.99	0.92–1.07

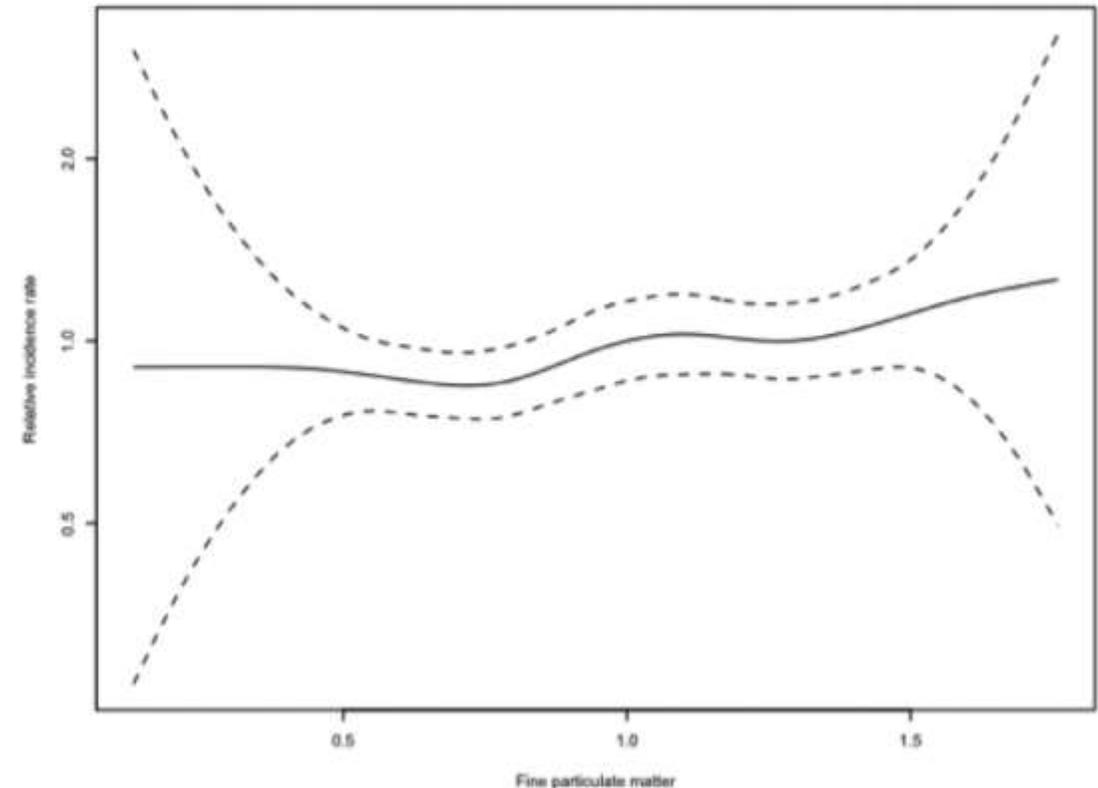
^a $\text{PM}_{2.5}$ concentrations were assigned to participants' place of residence at baseline based on remote-sensing data collected between 1998 and 2006.

^bUsing 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.

Residential exposure to fine particulate matter air pollution and incident breast cancer in a cohort of Canadian women

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PRE-MENOPAUSAL BREAST CANCER



Adjusted Rate Ratios, NO₂ and breast cancer (Goldberg et al, 2019 [under review])

Regression model	Premenopausal		Postmenopausal	
	Rate ratio	95% CI	Rate ratio	95% CI
	Age cut-off, 50 years			
Model I	1.13	0.98-1.30	1.04	1.00-1.08
Model II	1.15	0.99-1.33	1.03	0.99-1.07
Model III	1.15	0.99-1.33	1.03	0.99-1.07
Model IV	1.15	0.99-1.34	1.03	0.99-1.08
Model V	1.13	0.94-1.37	1.01	0.96-1.06
Model V + PM _{2.5}	1.09	0.89-1.35	1.01	0.96-1.07

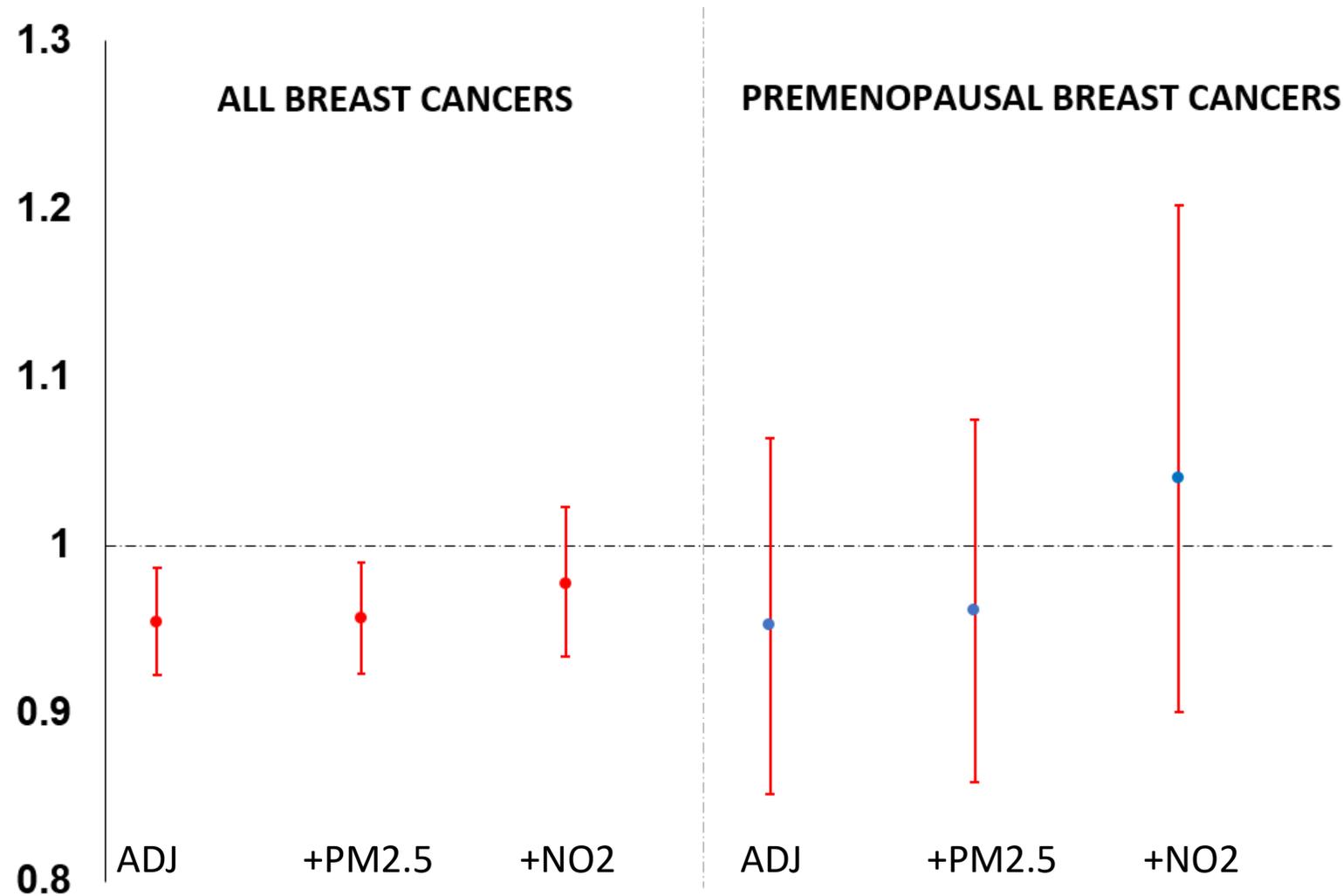
Table 4: Summary of adjusted effects of breast cancer studies in relation to a 5 ppb increase of NO₂

Study	No. of cases	Exposure methodology	Rate ratio per increase of 5 ppb (about 9.44 µg/m ³)	95% Confidence interval
		Postmenopausal women		
Montreal hospital-based c-c study) ⁶	383	Dense LUR assigned at time of interview	1.35	0.94-1.94
Montreal population-based c-c study ²⁶	679	Dense LUR assigned at time of interview	1.07	0.85-1.35
8-province c-c study ⁷	1,140	National LUR assigned at time of interview	1.03	0.93-1.15
Sister cohort (USA) ³³ ,	1,749	Spatial model using fixed-site monitors	1.02	0.97-1.06
Danish Nurses Cohort ³⁴ ,	1,145	Emissions/dispersion model	1.03	0.95-1.10
ESCAPE cohort (Europe, 15 cities) ⁸	3,612	LUR back extrapolated at time of entry	1.02	0.97-1.07
Present study (age cut-off of 52 years)	5,851	National LUR assigned at time of entry	1.00	0.98-1.02
		Premenopausal women		
8-province Canadian c-c study ⁷	619	National LUR assigned at time of interview	1.13	0.96-1.34
Present study (age cut-off of 52 years)	646	National LUR assigned at time of entry	1.09	1.07-1.11

Pearson Correlations

	PM2.5	Greenness	NO2
PM2.5	1.0	-0.14	0.56
Greenness		1.0	-0.55
NO2			1.0

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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