MAPPING THE RISK OF BREAST CANCER TO EXPOSURE FROM
TRAFFIC-RELATED AIR POLLUTION USING LAND-USE REGRESSION IN
VANCOUVER, B.C.

by

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Abstract

An environmental role in breast cancer etiology has been suspected but evidence is still inconclusive. Traffic-related air pollution is a potentially modifiable risk factor that has been studied in the etiology of breast cancer. Two Canadian studies using similar methodology to this study have recently reported positive associations between exposure to nitrogen dioxide (NO₂), a proxy for traffic-related air pollution, and breast cancer.

This thesis used land-use regression to estimate NO₂ exposure for 2,015 women recruited from Vancouver, British Columbia (BC) into a population-based case-control study conducted in 2005-2010. Cases were recruited from the BC Cancer Agency and controls from the Screening Mammography Program of BC. Cross-sectional and historical analyses were conducted using NO₂ estimated at time of study entry and ten years prior to study entry, respectively. Logistic regression models were created to estimate the relationship between exposure to NO₂ and breast cancer, adjusting for breast cancer risk factors and stratified by menopausal status. Sensitivity analyses were conducted, assessing potential biases introduced by screening mammography program attendance and immigrant status, among others.

The analysis at study entry included 964 cases and 945 controls. No association between NO₂ exposure (per 5 ppb increases) and risk of breast cancer was observed in the postmenopausal sample at study entry or at ten years prior to study entry. A consistent positive association in premenopausal women was observed at study entry (OR=1.17, 95% CI: 0.93, 1.48) and ten years prior to study entry (OR=1.18, 95% CI: 0.93, 1.49). The association between historical estimates of NO₂ (per 5 ppb increases) and breast cancer was stronger in a sensitivity

analysis excluding cases who had not attended screening mammography in the premenopausal sample (OR=1.20, 95% CI: 0.91, 1.59).

This study adds to the growing literature on exposure to traffic-related air pollution and breast cancer incidence. The results provide some support for the hypothesis that increased exposure may be associated with breast cancer, particularly in premenopausal women, although bias may have been introduced due to the selection of controls from a screening mammography program and low response rates. Future research, especially using prospective cohort studies, is needed.

Co-Authorship

This thesis represents the work of Nicollette Kwon in collaboration with her supervisors, Dr. Harriet Richardson, Dr. Michael McIsaac, and Dr. Dongmei Chen with additional input from Dr. Kristan J. Aronson, Dr. John J. Spinelli, and Dr. Mark Goldberg. The original study was designed and coordinated by Kristan Aronson, John Spinelli, Chris Bajdik, Angela Brooks-Wilson, Harriet Richardson, Igor Burstyn, Pierre Ayotte, Caroline Lohrisch, Sandip SenGupta, and Agnes Lai.

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List of Abbreviations

AIC	Akaike information criterion
BaP	Benzo[a]pyrene
BC	British Columbia
BMI	Body-mass index
CBCS	Canadian Breast Cancer Study
CI	Confidence interval
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen receptor
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
IDW	Inverse-distance weighted
GIS	Geographic information systems
GPS	Global positioning system
HER2	Human epidermal growth factor receptor 2
HRT	Hormone replacement therapy
LUR	Land-use regression
$\mu\text{g}/\text{m}^3$	micrograms per cubic meter
OC	Oral contraceptive
OR	Odds ratio
$\text{OR}_{5\text{ppb}}$	Odds ratio per 5 ppb increases
NO	Nitric oxide
NO ₂	Nitrogen dioxide
NO _x	Nitrogen oxides
NY	New York
PAH	Polycyclic aromatic hydrocarbon
ppb	parts-per-billion
PR	Progesterone receptor
RR	Relative risk
SES	Socio-economic status
SD	Standard deviation
SMP	Screening Mammography Program
TSP	Total suspended particulates
WEB	Western New York Exposures and Breast Cancer

Chapter 1

Introduction

1.1 Background and rationale

Breast cancer is the most common invasive cancer and the second-leading cause of cancer deaths among Canadian women (1). It is estimated that only one-third to one-half of new cases of breast cancer are attributable to the current established risk factors (2). These risk factors include demographic and socio-economic factors, reproductive factors, family history, and lifestyle factors, such as alcohol consumption, weight and height, and use of exogenous hormones (3). Occupational and environmental exposures that may have a possible role in breast cancer incidence have also been considered (2). A higher proportion of breast cancer cases may be attributable to the interaction of various lifestyle risk factors and environmental or occupational exposures (2). Most of these risk factors confer very modest elevated risks (except family history of breast cancer, ionizing radiation, benign breast disease, and breast density) (3). This establishes a need for additional research into other possible etiologic agents and environmental exposures, such as traffic-related air pollution.

Several ecologic studies have shown elevated risks for developing breast cancer in areas of high urbanization (4-6), and therefore, higher exposures of traffic-related air pollution, industrial pollutants, and other environmental toxins. Significantly higher risks of breast cancer were observed for clusters within southern Ontario: specifically, in the counties of Toronto and Niagara, there were elevated relative risks ranging from 1.15 to 1.29 (5). These risks may be attributable to higher levels of industrial pollution or agricultural chemicals such as pesticides and fungicides (5). Regional variation in breast cancer risk has also been observed in the United

States (7). A study using ecologic-level data of air pollutant emissions and breast cancer incidence rates observed incidence rates of breast cancer to be significantly higher in metropolitan areas compared to non-metropolitan areas (8).

In October of 2013, the International Agency for Research on Cancer (IARC) announced outdoor air pollution as a Group 1 definite carcinogen to humans (9). IARC concluded that there is sufficient evidence that exposure to air pollution causes lung cancer and also evidence of an increased risk of bladder cancer (9). Outdoor air pollution is an incredibly widespread environmental carcinogen which also has a conclusive and causal negative impact on general health.

Historically, exposure to air pollution has been associated with increased risks for lung cancer (10) and respiratory diseases (10,11), but there is now emerging evidence to suggest an association between traffic-related air pollution and increased risks for breast cancer (8,12-15), as well as brain (15) and cervical cancer (15). Components of traffic-related air pollution, polycyclic aromatic hydrocarbons (PAHs), have been suggested to be the biologic agents in breast cancer carcinogenesis (14,16-18). Several PAHs, including benzo[a]pyrene and dibenzo[a,l]pyrene, are well-established mammary carcinogens in animal models (18). As traffic-related air pollution is an extremely ubiquitous exposure, its potential carcinogenicity has a wide-reaching audience and therefore, is a public health concern.

This will be the third Canadian study which uses an exposure assessment method known as land-use regression (LUR) to assess the relationship between traffic-related air pollution and breast cancer. The first was a study conducted in Montreal, Quebec by Crouse et al. which assessed the risk of air pollution on postmenopausal breast cancer. An odds ratio (OR) of 1.31 was observed for every 5 parts-per-billion (ppb) increase in estimated nitrogen dioxide (NO₂)

exposure at time of study entry ($OR_{5ppb}=1.31$, 95% confidence interval (CI): 1.00, 1.71) (14).

The second study was based on data collected from a national case-control study conducted between 1994 and 1997 (19). Hystad and collaborators (20) used three different exposure measures to characterize exposure to traffic-related air pollution: two involving satellite-derived observations and the third using a national land-use regression model. The study reported an odds ratio of 1.07 per 10 ppb increases in NO_2 (95% CI: 0.86, 1.32) for postmenopausal breast cancer and an odds ratio of 1.28 per 10 ppb increases in NO_2 (95% CI: 0.92, 1.79) for premenopausal breast cancer using the land-use regression estimates for exposure. In this thesis project, exposure to NO_2 at time of study entry and at ten years prior to study entry will be derived from a land-use regression model created by Henderson et al. in 2003 (21).

Similar to the study in Montreal, odds ratios for 5 ppb increases in NO_2 exposure will be calculated for the sample of women; analyses will be stratified by menopausal status to make direct comparisons to the Montreal sample of postmenopausal women and both samples of premenopausal and postmenopausal women in the national study, as well as to assess risk of breast cancer by menopausal status in Vancouver women.

1.2 Overview of study design

This study attempts to further understand the possible role of traffic-related air pollution in the etiology of breast cancer using an exposure assessment method known as land-use regression to assign air pollution exposure to women with and without breast cancer. These women were recruited into the Canadian Breast Cancer Study (formerly known as the Molecular Epidemiology Breast Cancer study), which was a case-control study conducted in Vancouver, British Columbia and in Kingston, Ontario by Aronson et al., from 2005 to 2010. It aimed to

identify genetic, lifestyle, and environmental risk factors for breast cancer. Participants were given a questionnaire to complete and a blood or saliva sample was collected. In this thesis project, only women from Vancouver will be included in the analysis.

1.3 Objectives

The primary objective of this thesis was to assess the association between traffic-related air pollution exposure and breast cancer. This association was examined using exposures estimated separately at two time points (at study entry and ten years prior to study entry) to assess the latency in breast cancer development. This thesis also describes the differences in identified risk factors for breast cancer among cases and controls. Several sensitivity analyses were conducted to assess the effects of certain methodological decisions. Specifically, these include analyses excluding cases who had entered the study after two years of their diagnosis of breast cancer to address potential “incidence-prevalence” bias, excluding participants with more than one residence for the ten years before their study entry to reduce misclassification based on address, excluding cases who had never attended screening mammography to reduce potential selection bias, and excluding participants who were not born in Canada to reduce the “healthy immigrant” effect.

1.4 Thesis organization

The second chapter in this thesis reviews the current body of literature on the relationship between breast cancer and traffic-related air pollution. It also describes factors which are independently associated with breast cancer and traffic-related air pollution, as well as

challenges in assessing exposure to air pollution. The third chapter outlines data collection procedures, methods used by Henderson et al. (21) to create the land-use regression model, geospatial programming to assess NO₂ exposure, categorization of all covariates, and statistical analyses used in examining the relationship between breast cancer and traffic-related air pollution. The fourth chapter describes the results of the data analysis objectives. The fifth and last chapter contains a general discussion on the findings in the fourth chapter, as well as strengths and limitations of this thesis project, future research directions, and overall conclusions.

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Chapter 2

Literature Review

2.1 Epidemiology of breast cancer

Breast cancer is the most common invasive cancer and the second-leading cause of cancer deaths among Canadian women (1). In 2014, 24,400 new cases of breast cancer and 5,000 deaths were expected in Canada, accounting for approximately 26% of new female cancer cases and 14% of female deaths (1). There are a number of well-established risk factors for breast cancer which are explained in more detail below (see Section 2.2). These risk factors include demographic factors, reproductive factors, genetic factors, and lifestyle factors. Some occupational and environmental factors have also been observed to increase risk of breast cancer.

In Canada, the age-standardized incidence rate of breast cancer in 2014 was estimated to be 99.2 cases per 100,000 (1). The highest incidence rate by province is 101 cases per 100,000 in Ontario, Quebec, and Nova Scotia (1). The lowest are found in Prince Edward Island, New Brunswick, and Newfoundland (95, 93, and 82 cases per 100,000, respectively) (1).

As knowledge of the molecular biology of breast cancer advances, breast cancer is no longer thought of as a single disease. Breast cancer consists of a number of specific subtypes, distinguished by a woman's menopausal status when diagnosed and tumour receptor status. A few factors which are known to increase the risk of postmenopausal breast cancer have null or inverse effects on premenopausal breast cancer (eg, greater body-mass index (BMI) is protective against breast cancer in premenopausal women (relative risk (RR)=0.58 for women with a BMI > 31 kg/m² compared to women with a BMI < 21 kg/m², 95% CI: 0.40, 0.83) and is a risk factor for postmenopausal women (RR=1.25 for women with a BMI > 28 kg/m² compared to women with a BMI < 21 kg/m², 95% CI: 1.02, 1.52) (2). Tumour receptors include those which respond

to hormones, estrogen, progesterone, and HER2 (human epidermal growth factor receptor 2) (3). Depending on tumour receptor status, treatment options and benefits vary (eg, triple negative breast cancers are estrogen-receptor negative, progesterone-receptor negative, and HER2-receptor negative tumours and respond poorly to hormonal and targeted therapies).

2.2 Breast cancer risk factors

There are a number of breast cancer risk factors which are considered potential confounders in the relationship between traffic-related air pollution and breast cancer. These include non-modifiable factors (relating to genetics, demographics, socio-economic status (SES), and the reproductive cycle) and modifiable factors (relating to health and lifestyle).

Generally, non-modifiable risk factors relate to demographics, SES, reproductive history, and family history of breast cancer. Higher age, white or Western ethnicity, higher education, and higher income are all associated with an increased risk of breast cancer (4). The highest incidence rates for breast cancer are observed in developed, Western countries such as the United States and Canada, while the lowest incidence rates are observed in Asian countries and less developed countries (4).

Factors related to the reproductive cycle are also well-established as risk factors. Early age at menarche or menstruation (1.1 to 1.9-fold increased risk in those ≤ 11 compared to ≥ 15 years) (5,6), late age at first full-term pregnancy (1 to 2-fold increased risk in those > 30 years compared to < 20 years) (5,7-10) nulliparity or having no children (1 to 2-fold increased risk in those without children compared to those with) (4), and late age at menopause (1.1 to 1.9-fold increased risk in those ≥ 55 compared to those ≤ 45 years) (5,6) are shown to consistently increase risk for breast cancer. Having higher parity (0.5-fold decreased risk for those with ≥ 5

children compared to those with none) (11,12) and breastfeeding (RR decreased by 4.3%, 95% CI: 2.9, 5.8 for every 12 months of breastfeeding) (13) are protective against breast cancer.

These factors are thought to represent cumulative exposure to endogenous estrogen, a hormone produced in the body which induces cell proliferation) (14). A related procedure is oophorectomy (removal of one or both ovaries), which greatly reduces levels of endogenous estrogen. If this procedure is performed before the age of 35 (for bilateral oophorectomy) or 45 (for unilateral oophorectomy), breast cancer risk is thought to be reduced (14).

Genetic factors include family history and gene variants. A woman with more first-degree relatives (ie, mothers, sisters, daughters) with breast cancer is at higher risk of being diagnosed with breast cancer herself (RR=2.6 for those with a family history of breast cancer compared to those without) (7). This risk increases if the relative's breast cancer is premenopausal. Gene variants such as the BRCA1 and BRCA2 mutations are identified as strong risk factors of breast cancer. These mutations are rare in the general population, but may occur at higher rates in certain ethnic groups (eg, in Ashkenazi Jews) (4). Some low-penetrance genes variants, which induce weaker risks but are more common in the general population, have also been identified.

Modifiable risk factors include lifestyle and health factors (eg, BMI, weight, height, diet, alcohol consumption, tobacco smoking, and use of hormonal medications). BMI (body-mass index) is a summary measure of weight and height and is used in defining obesity. Obesity has differing effects on breast cancer risk with menopausal status. Obesity (BMI greater than 30 kg/m²) and weight gain increase the risk of postmenopausal breast cancer (8% increase in risk per 5 kg increases in adult weight gain) (15-18), while having higher BMI protects against premenopausal breast cancer (RR=0.94, 95% CI: 0.92, 0.95 per 2 kg/m² increases) (19,20).

Increased height is considered an independent factor which weakly increases risk in postmenopausal women (RR=1.07, 95% CI: 1.03, 1.12 per 5 cm increases in height) (2).

Increased height is thought to be an indicator of high energy intake during childhood (18). While increased consumption of well-done or charred meats and unsaturated fatty acids, have been observed to confer increased risks (4), there is inconsistent evidence for any one dietary factor except for alcohol consumption (21,22). Risk of breast cancer increases 10% for every 10 g (approximately 1 drink) of alcohol consumed per day (4,20). The IARC found limited evidence for the carcinogenicity of tobacco smoking for female breast cancer (23). A pooled analysis of data from 53 studies, with over 58,000 cases and 95,000 controls, found that smoking was not associated with breast cancer (24). Use of oral contraceptives (OC) and hormone replacement therapy (HRT) increases exposure to exogenous hormones and is associated with increased risk of breast cancer, especially in postmenopausal women (4). Current users of oral contraceptives have a 24% increase in risk (25). Women who are currently using OC have the highest risks of breast cancer and this risk decreases with increasing years after stopping use (25).

In addition to lifestyle-related risk factors, occupational and environmental risk factors have been associated with increased risk of breast cancer. There is consistent evidence for increased risk with exposures to ionizing radiation (22) and for women whose occupations involve shift work, which disrupts the circadian rhythm system (26). Women who worked night shifts for a long period of time had a strong increase in risk (RR=1.48, 95% CI: 1.36, 1.61) (26). In another study, an odds ratio of 2.21 was reported for women who were employed in shift work for over 30 years compared to women who never did shift work (95% CI: 1.14, 4.31) (27).

2.3 Ambient air pollution

Air pollution is now widely accepted to be associated with mortality and various diseases, including asthma, chronic bronchitis, emphysema, cardiovascular disease, and lung cancer (28). Ambient or outdoor air pollution has recently been classified as a definite (Group 1) human carcinogen by the International Agency for Research on Cancer (IARC) (29). Ambient air pollution is composed of natural pollution (eg, volcanoes, forest fires) and anthropogenic pollution (30). The latter can be further divided into combustion sources, industrial processes, and processes related to mining and drilling (30). Air pollutants produced from combustion (burning fossil fuels for power, heat, or transportation) includes sulfur oxides, nitrogen oxides, carbon monoxide, carbon dioxide, smoke, volatile organic compounds, polycyclic aromatic hydrocarbons, and particulate matter (30). In urban areas, the main source of ambient air pollution is from motor vehicle exhaust (30,31). Many components of traffic-related air pollution, such as particulate matter and specific polycyclic aromatic hydrocarbons, have also been classified as either definite or probable (Group 2A) human carcinogens (31). In urban areas, the main source of ambient air pollution is from motor vehicle exhaust (32,33).

Nitrogen dioxide (NO₂) is measured routinely by environmental regulation agencies in major cities in Canada. NO₂ is commonly used as a proxy measure for traffic-related air pollution and was suggested as the “best indicator among pollutants monitored of fresh combustion” (32). NO₂ is considered a good indicator of traffic-related pollution trends due to its high collocational association with other pollutants (such as PAHs) (34); and this has also been found in Canada (32). It is also inexpensive and easy to measure directly with passive samplers (35,36). A study in Montreal, Quebec assessed 23 air pollutants for spatial and temporal variability and although the authors concluded that there is no one single “perfect” proxy

measure for air pollution, the nitrogen species (NO, NO₂, NO_x), being strongly correlated to traffic emissions in cities and easily measured, can be considered the best available indicator of spatial variation in exposure to traffic-related air pollution (37).

2.3.1 Challenges in measuring air pollution

Many methods to capture variability in air pollution have been developed and used to varying degrees of success in the literature. Pollution exposure can be measured directly or indirectly at the individual-level or at the ecologic-level (38). The first published air pollution epidemiology studies characterized exposure ecologically as average annual concentrations and compared mortality rates between cities (39). However, associations found by measuring air pollution at the ecologic-level (through regulatory monitors) are subject to ecologic fallacy. Since then, it has become known that within-city variability in air pollution concentrations, especially NO₂, is as great as or greater than between-city variability (39). Over the last 20 years, air pollution exposure assessment methods have been refined to estimate exposure at the individual-level (28).

Directly measuring exposure to air pollution at the individual-level will produce more accurate measurements of exposure (28). This can be done through measuring pollutant concentrations with personal monitors and global positioning systems (GPS) locators or by measuring biomarkers, which are indicators of personal exposures interacting with biological systems (28). Both methods are expensive to employ and impractical for long-term exposure and therefore are of limited use.

Air pollution exposures can be indirectly measured through the use of exposure indicator variables (eg, traffic intensity, proximity to roads), interpolation methods (eg, kriging, inverse distance weighting), conventional dispersion methods, and land-use regression models (39). The use of exposure indicator variables as a proxy for exposure is much cruder than the other methods, but this was confirmed as a valid estimate of exposure to traffic-related air pollutants (28). Interpolation methods use stochastic modeling to estimate pollution concentrations from monitored pollutant measurements (40) while dispersion methods use emission data on stationary pollution sources (eg, home heating), mobile pollution sources (estimated by traffic indicator variables), and meteorological data (such as air temperature and wind speeds) to predict spatial and temporal concentrations. This method is relatively costly, due to data input and high GIS (geographic information systems) expertise requirements; although when used in conjunction with GIS, it is able to predict air pollution in a study area without needing passive monitoring of pollutants (40). Land-use regression (LUR) combines pollutant measurements with a number of predictor variables related to the geography of the region of interest in a stochastic model to predict exposure. Since regulatory monitor measurements alone do not capture the within-city variability, land-use regression requires additional passive monitoring (multiple daily or weekly samples) (39). This method also uses GIS which enables many unique and useful abilities in data collection and representation, location, spatial analysis, and visualization (28).

The methods used to create the LUR model used in this thesis project will be described in a later section (see Section 3.5). A 2008 study evaluated the performance of the LUR model in predicting personal exposure measurements (41). A small sample of women was given personal monitors and GPS data-loggers to estimate personal exposure to NO₂. They were also assigned

an NO₂ exposure using the LUR model and their home residence. The study found that the LUR estimates were less varied than the personal measurements and demonstrated moderate correlations between the two. The LUR showed the stronger ability to predict the NO₂ personal measures when compared to the other methods of exposure assessment conducted in the study (distance to nearest ambient monitor and inverse-distance weighted interpolation) (41).

2.3.2 Determinants of traffic-related air pollution

Concentrations of traffic-related air pollution are influenced by the type of vehicle, vehicle speeds, fuel types and quality found in the area and traffic congestion levels (42) . Environmental factors such as meteorological conditions, topography, and built environment can also affect traffic-related air pollutants. Depending on which chemical compounds are found in the atmosphere, chemical reactions occur with traffic-related air pollutants which may dilute the concentrations measured.

These factors are taken into consideration in the land-use regression model created for the region of Metro Vancouver. More detail on the land-use regression model can be found in Section 3.5.1.

2.4 Traffic-related air pollution and breast cancer

2.4.1 Proposed biologic mechanisms

This thesis project is investigating the role of traffic-related air pollution in breast cancer etiology using NO₂ to estimate exposure. While some studies have shown associations between exposure to traffic-related air pollution and increased risk of breast cancer, it is still not known

which compound or compounds in air pollution may be responsible. It is suggested that polycyclic aromatic hydrocarbons (PAHs), a chemical compound found in the ambient environment and in the human diet (43), is involved in breast cancer carcinogenesis (33,43-45).

Polycyclic aromatic hydrocarbons are organic compounds which consist of systems of fused aromatic rings (46). Exposure to PAHs can be attributable to occupational, environmental, and dietary sources (47). PAHs are produced from incomplete combustion of fossil fuels (eg, gasoline or diesel in transport vehicles, coal in industrial processes) (46). They can also be found in the diet (on the surface of charred or well-done meat) and in cigarette smoke (44). They are known to be highly mutagenic, lipophilic, carcinogenic, and immunotoxic (46). Several PAHs, including benzo[a]pyrene and dibenzo[a,l]pyrene, are well-established mammary carcinogens in animal models (45).

Due to their lipophilic properties, PAHs can be stored in human milk, blood, placenta, and other fat tissues, such as the breast (48). They may reach elevated concentrations and induce carcinogenesis in the breast (33).

PAHs are genotoxic and can react with DNA to form PAH-DNA adducts. PAH-DNA adducts are formed with high exposure to PAHs and are fixed by DNA repair mechanisms; levels of PAH-DNA adducts in the blood are therefore indicators of exposure levels and DNA repair system adequacy (44,45). Damage to DNA due to PAH-DNA adduct formation has been hypothesized to induce mutations in tumour suppressor genes and proto-oncogenes, increasing the risk of tumour formation and cancer risk (45).

PAHs also have estrogenic properties (ie, having similar properties as estrogen) and may mimic estrogen as an agent in cell proliferation, increasing breast cancer risk (33,44,49).

2.4.2 Epidemiologic evidence

Numerous epidemiologic studies have looked at the risk of cancers and other chronic diseases and traffic-related air pollution. Historically, increased risks for lung cancer (50,51) and respiratory diseases (50,52) have been associated with air pollution, but there is emerging evidence to suggest an association between traffic-related air pollution and increased risks for breast (33,49,53-55), brain (55), and cervical cancers (51). As traffic-related air pollution is a ubiquitous exposure, its potential carcinogenicity has a wide-reaching audience and therefore, is of public health concern.

Studies investigating the role of traffic-related air pollution have used different techniques to capture exposure. Methods assess exposure at the ecologic-level (eg, assessing study areas by their urban or rural status), at the individual-level, using personal monitors or residential histories, or at the individual-level controlling for ecology-level factors. This section will summarize the state of the epidemiologic literature by exposure assessment used.

2.4.2.1 Ecologic studies

A number of ecologic studies have shown associations between increased breast cancer incidence and measures of air pollution. In 2012, a study was conducted using ecological ambient air pollution and breast cancer incidence data in the United States (53). Associations between time trends and regional variations of air pollutant emissions and increased incidence of breast cancer were found between 1986 and 2002. Positive correlations between emissions of various air pollutants and breast cancer incidence were also observed (NO_x $r=0.89$, CO $r=0.82$,

SO₂ $r=0.71$, $p < 0.001$) (53). A study using breast cancer incidence trends from SEER found positive associations with monitored nitrogen oxides and traffic density in 28 counties in the United States (56). Geographic areas with higher traffic density (> 13 vehicles/mi²) had a significant higher risk of breast cancer incidence than areas with low traffic density (< 0.9 vehicles/mi²) (56). Another ecologic study assessed breast cancer incidence by urban and rural regional status across six years in Egypt (57). Incident cases were identified from the Gharbiah population-based cancer registry from 2001 to 2006 and addresses were linked with census data to determine urban or rural status. Incidence of breast cancer was higher in urban areas compared to rural areas and this association persisted when breast cancers were stratified by hormonal receptor subtype. In a somewhat similar study conducted in the Netherlands, risk of breast cancer incidence was examined in areas of varying urbanization (58). Classification of urbanized areas was determined by address density (defined as “the number of addresses within a radius of 1 km of an average address in the area”). For example, very dense urbanized areas had $> 2,500$ addresses/km² while sparsely urbanized areas had 500 to $< 1,000$ addresses/km². Breast cancer incidence was marginally increased for each type of urbanized area compared to non-urban areas (OR=1.07, 95% CI: 1.03, 1.11, for very dense urbanization compared to non-urban areas) (58). Urban areas are thought to have higher concentrations of air pollutants and occupational hazards than rural areas. With all ecologic studies, it is important to interpret results while considering ecologic fallacy. Associations using ecologic-level data may be explained by individual-level differences which these studies cannot account for, such as age at menarche, parity, or education. In the Netherlands study, authors stated that newly adopted screening programs may have confounded the relationship between breast cancer incidence and urbanization (58). Higher rates

of screening mammography in urban regions may result in higher rates of breast cancer detection compared to non-urban regions (59).

2.4.2.2 Exposure modelling

The exposure assessment methods used in the following studies feature exposure modeling using spatiotemporal techniques, usually based in GIS. These include proximity models, dispersion models, land-use regression models, interpolation models, and hybrid models. Generally, these models are made to simulate pollutant concentrations that an individual would have been exposed to (28). More refined methods (eg, land-use regression) will produce a model which includes additional information on factors which influence pollutant concentrations. Each method makes assumptions about pollutant concentrations which are limited (eg, in proximity models, the assumption is the closer the proximity, the greater the exposure) (28). Two studies were conducted in the Erie and Niagara counties in New York State (49,54). Bonner et al. employed an inverse-distance weighted interpolation technique to estimate total suspended particulates (TSP) (49). TSP measurements were taken from regulatory fixed-site monitors from 1959 to 1997 and models were created for the 1960s and each year after until 1997. The highest quartile ($> 140 \mu\text{g}/\text{m}^3$) of TSP compared to the lowest ($< 84 \mu\text{g}/\text{m}^3$) was associated with an odds ratio of 2.42 (95% CI: 0.97, 6.09, adjusted for age, education, and parity) with suggested significance in postmenopausal women with exposures estimated for time of birth. All other associations presented (at time of birth, menarche, first birth, for both premenopausal and postmenopausal breast cancer) were null with no clear trends. While a strength of this study is its ability to estimate historical exposures in a women's past, the measurements used to model the exposure were taken from fixed-site monitors, placed in areas of high pollution which require

monitoring (49). The interpolation method used also does not take into consideration additional factors which influences TSP dispersion patterns. Therefore the estimates for each women are potentially misclassified. There is potential for geographic selection bias in this study, as authors found that cases and controls were more likely to live closely to the study site than otherwise expected (49). In a follow-up study, Nie et al. used dispersion modeling to estimate a specific PAH, benzo[a]pyrene (BaP) for the same critical time periods (54). An odds ratio of 2.05 (95% CI: 0.92, 4.54, adjusted for age, race, education, age at first birth, and year at interview) was observed for premenopausal women with high BaP exposure measured at time of menarche (highest quartile compared to the lowest) (54). High BaP exposure measured at time of first birth (highest quartile compared to the lowest) was associated with increased risk of postmenopausal breast cancer (OR=2.57, 95% CI: 1.16, 5.69, adjusted for age, race, education, age at first birth, and year at interview) (54). This dispersion model is a more refined method of exposure assessment than the interpolation model used in the Bonner study: it took into account various meteorological conditions, traffic flow, and seasonal differences in traffic emissions (60). The same participants were used in this study, so the same geographic selection bias may be a concern (54).

Occupational exposure to benzene and PAHs was assessed for increased risk of breast cancer in premenopausal women in Montreal (61). Job-exposure matrices and occupational histories were used to estimate exposures for cases identified from hospitals and for controls recruited randomly from the New York State Department of Motor Vehicles. Response rates were 66% and 62% for cases and controls respectively. Women who had high probabilities of being exposed to benzene and PAHs were at an increased risk of breast cancer (OR=1.95, 95% CI: 1.14, 3.33, OR=2.40, 95% CI: 0.96, 6.01, respectively); however, risks related to PAH

exposure could not be examined independently of benzene exposure so results are somewhat inconclusive. Examples of occupations with higher PAH exposure include bus, truck, and stationary engine mechanics and traffic, shipping, and receiving clerks (61).

Currently, there are only two Canadian studies which used land-use regression (LUR) to determine exposure to traffic-related air pollution and assessed risk of breast cancer: one was conducted in Montreal, Quebec (33) while the other used data from a nation-wide Canadian case-control study (62). Crouse and collaborators created land-use regression models using lifetime residential histories. Three NO₂ exposures were estimated: at time of the LUR model creation (2005/6), study entry (1996/7), and approximately ten years prior (1985). This was a hospital-based case-control study of incident, invasive cases of postmenopausal breast cancer. Controls were individuals with incident cancers other than breast and were matched to cases by hospital and frequency-matched by age. Exposure to NO₂ at time of study entry was associated with increased risk of postmenopausal breast cancer (OR= 1.31 per 5 ppb increases in NO₂, 95% CI: 1.00, 1.71). A sensitivity analysis was conducted for subjects who resided in one residence for at least ten years and observed similar odds ratios but with wider confidence intervals (due to smaller sample sizes). Effect estimates were adjusted for hospital of diagnosis, family history of breast cancer, oophorectomy, education, ethnicity, age at menarche, age at first full-term pregnancy, breastfeeding history, oral contraceptive use, hormone replacement therapy use, BMI, exposure to tobacco smoke, respondent/proxy status, alcohol consumption, history of benign breast disease, various occupational exposures, and median household income and percentage of adults without a high school diploma at the census tract level (33).

Hystad and colleagues used similar methodology to that used in this thesis project and in the Montreal study (62). Eight of the ten provinces in Canada participated in a population-based

case-control study and a total 1,569 breast cancer cases and 1,872 controls were recruited (63). Cases were recruited randomly from each provincial cancer agency. Controls were recruited differently in each province, either using provincial health insurance plans (PEI, Nova Scotia, Manitoba, Saskatchewan, BC), the Ministry of Finance Property Assessment database (Ontario), or random-digit dialing (Newfoundland and Alberta). Participants had to have reported at least 90% complete residential histories from 1975 to 1994 for inclusion in this study. NO₂ exposure levels were then estimated for this time period using the land-use regression model created for the entire country. Two additional exposure measures were used to characterize exposure to traffic-related air pollution involving satellite-derived observations, however, only the results from the land-use regression model will be described here. The study observed positive, non-significant associations (OR=1.07, 95% CI: 0.86, 1.32 and OR=1.28, 95% CI: 0.92, 1.79) for 10 ppb increases in NO₂ and post- and premenopausal breast cancer, respectively. Models were adjusted for a number of established and suspected risk factors for breast cancer, as well as age and study province: age at menarche, years of menstruation, parity, age at first full-term pregnancy, breastfeeding, bilateral oophorectomy, BMI, smoking, alcohol consumption, median household income, years of education, residential and occupational second-hand smoke exposure, meat and vegetable consumption, physical activity, mammography screening, neighbourhood-level socioeconomic deprivation, and urban living status (62).

2.4.2.3 Personal exposure measurements

A more accurate method of deriving exposure estimates is by directly measuring concentrations of pollutants. This can be done by measuring metabolites in biologic samples or by measuring pollutant concentrations using personal monitors. DNA adducts are often measured

as a biologically effective carcinogen dose (64). They represent the metabolized internal dose that has reacted with DNA and has not yet been repaired, and are therefore a product of an individual's metabolism and repair systems as well as exposure. Several studies have examined DNA adducts as a byproduct of environmental pollutant exposure in relation to breast cancer risk. Rundle et al. conducted a hospital-based case-control study of 100 breast cancer cases and 105 controls with benign breast disease (65). PAH-DNA adducts were measured using immunohistochemical assays in cancerous and non-cancerous breast tissue from the cases and normal breast tissue from the controls. This study found a positive association for increased DNA adducts in tumour tissue compared to control tissue after controlling for potential confounders (OR=2.56, 95% CI: 1.05, 6.24) (65). However, there may be a potential bias from using controls with benign breast disease, as the prevalence of family history of breast cancer in this population is much higher than in women without a history of benign breast disease (66). Gammon et al. conducted several studies on Long Island in New York, measuring DNA adducts from pesticide and PAH exposure (67-69). Blood levels of organochlorines did not differ between cases and controls and age-adjusted and multivariate-adjusted ORs (highest quintile compared to lowest) were weak (eg, for one organochlorine, DDT, OR=1.15, 95% CI: 0.74, 1.79) and not statistically significant.

In general, studies that examined organochlorine pesticide levels in adipose tissue and in blood samples in relation to breast cancer incidence have found inconclusive results (70). In the same Long Island, NY study population, breast cancer incidence was found to be associated with detectable PAH-DNA adducts in blood samples compared to non-detectable DNA adducts (age-adjusted OR=1.29, 95% CI: 1.05, 1.58) (69). When stratified by menopausal status, postmenopausal breast cancer was not associated with detectable DNA adducts while

premenopausal breast cancer was. The biggest limitation in using biomarkers to determine pollution exposure is that the time period of exposure estimation is never relevant to disease causation. Biomarkers are a product of too recent exposure in the case of long-term diseases, such as breast cancer (70,71).

2.5 Summary of rationale

Traffic-related air pollution is a major concern in urban areas; exposures to air pollutants have been associated with a variety of health outcomes, including headaches, nausea, acute and chronic respiratory effects, heart disease, and several cancers. Breast cancer incidence cannot be fully explained by the current established risk factors and there exists a need for further etiological research into environmental exposures. This study uses a refined exposure assessment method known as land-use regression to estimate exposure to traffic-related air pollution to assess the risk of breast cancer incidence in Vancouver, British Columbia.

The International Agency for Research on Cancer (IARC) classified outdoor air pollution as a Group 1 or definite human carcinogen (29). Several ecologic studies have shown increased risk of breast cancer in areas of high urbanization (57,57,58,72,73), and therefore, higher exposures of traffic-related air pollution, industrial pollutants, and other environmental toxins, such as pesticides. Several case-control studies have examined the relationship between traffic-related air pollutants and breast cancer in Canada (33,62), Erie and Niagara counties in New York State (49,54), and in Long Island, New York (74). Additionally, there have been several studies which have measured PAH-DNA adducts, a marker of DNA damage and thought to be one of the possible carcinogenic agents within air pollution (43,65-67,69). However these studies all suffer from limitations: these include using ecologic-level data and being subject to the

ecologic fallacy, using inadequate comparison groups which may have compromised internal validity, using measurements which may not have fully captured the true geographic distribution of the exposure, and using biomarkers which may introduce misclassification, as the exposure being assigned is a measure of recent exposure rather than cumulative exposure.

This thesis project examined the association between breast cancer and traffic-related air pollution using data from a Vancouver based case control study in both pre- and postmenopausal women. NO₂ was estimated using land-use regression and residential histories at time of study entry and ten years prior. This will be the third study of its kind and aims to build on the work of two prior Canadian studies (33,62).

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Chapter 3

Methods

3.1 Objectives

The primary objective of this thesis was to assess the association between traffic-related air pollution exposure and breast cancer. This association was examined with air pollution exposure estimated at two time points (at study entry and ten years prior to study entry) to assess the latency in breast cancer development. This thesis also described the differences in established risk factors for breast cancer among cases and controls. Several sensitivity analyses were conducted to assess the effects of certain methodological decisions.

3.2 Study design

The Canadian Breast Cancer Study (CBCS) (formerly known as the Molecular Epidemiology Breast Cancer study) was a case-control study conducted in Vancouver, British Columbia and in Kingston, Ontario by Aronson et al. (1), from 2005 to 2010. It aimed to identify genetic, lifestyle, and environmental risk factors for breast cancer. To do so, a questionnaire was completed by participants (see Appendix B) and a blood or saliva sample was collected at time of study entry.

3.3 Original study population

Cases and controls were originally recruited for the Canadian Breast Cancer Study (formerly known as the Molecular Epidemiology Breast Cancer Study). From 2005-2010, 2,077

women were recruited from Vancouver, British Columbia (BC) and 295 women from Kingston, Ontario. For this project, only participants from Vancouver (1,001 cases and 1,014 controls) will be analyzed. Cases were recruited from the BC Cancer Agency with *in situ* or invasive breast cancer. These women were 20-80 years old, had no previous cancer history (except non-melanoma skin cancer), and lived in Vancouver or its surrounding communities (New Westminister, Richmond, and Burnaby). Controls were cancer-free individuals recruited from the Screening Mammography Program (SMP) of BC. These women were recruited from breast screening clinics in the same geographic locations as cases and had agreed to participate in research studies over the course of their routine screening. Cases and controls were frequency-matched by a five-year age group.

If consent was given, blood and/or saliva samples were taken and access to medical health records was granted. Response rates of those who consented to being contacted were 54% for cases and 57% for controls. Women aged 40-79 are considered eligible for the screening program in BC, so cases under the age of 40 were excluded. Additional cases were excluded because their cancer diagnosis date occurred prior to study entry. This resulted in a final sample size of 1,001 and 1,014 eligible cases and controls, respectively.

Ethics approval for the main study was obtained from the University of British Columbia – BC Cancer Agency Ethics Board and from the Queen’s University Health Sciences Research Ethics Board. Ethics approval for this student project was obtained from the Queen’s University Health Sciences Research Ethics Board.

3.4 Data collection procedures

The questionnaire given to participants (Appendix B) collected information on demographics, education, ethnicity, medical and reproductive history, family history of cancer, lifestyle characteristics (including smoking and alcohol habits), lifetime physical activity, cooking habits, and lifetime occupational and residential histories. Questionnaires were self-administered or conducted by interview in English, Cantonese, Mandarin, or Punjabi.

3.5 Exposure

The exposure in this thesis project is nitrogen dioxide (NO₂). Average annual nitrogen dioxide exposure was estimated for each participant using their home residential history and a land-use regression model created for the region of Metro Vancouver in 2003. Nitrogen dioxide is considered a proxy for exposure to traffic-related air pollution in this study.

3.5.1 Land-use regression

Land-use regression (LUR) is an exposure assessment method that combines measured pollutant concentrations, characteristics of land-use, traffic, and geography in a least-squares model that estimates pollutant concentrations across the area of a specific region. The model is adapted to each region of interest which improves concentration predictions, since areas which may require additional monitoring can be identified (2). Land-use regression requires the use of geographic information systems (GIS) which can help minimize potential misclassification in exposure assignment (3).

This thesis project used a nitrogen dioxide land-use regression model developed for the region of Metro Vancouver, created in 2003 by Henderson et al. (4). In brief, the procedure of the creation of the LUR model is outlined below.

A location-allocation model was created to identify 100 sites whose measurements would optimize variability in pollutant concentrations in Vancouver. This model used five years of regulatory data as input. A two-step algorithm was involved which first built a demand surface and then determined 100 optimal locations for NO₂ sampling. An additional 16 sites were added to capture concentrations in specific areas of interest. The LUR domain covered 2,200 km² of the Greater Metropolitan Area of Vancouver (Metro Vancouver).

To capture the seasonality of NO₂ concentrations, historical regulatory NO₂ data were analyzed and two 2-week sampling periods were identified as optimal. The combined means from each sampling period were within 15% of the annual average. These sampling periods ran between February 24 through March 14 and September 8 through September 26 in 2003. The measured concentrations from each sampling period were averaged to estimate the annual mean for each site. The spring and fall mean concentrations were 19.6 (SD=4.9) and 12.9 (SD=4.1) parts per billion (ppb), respectively. These concentrations were averaged to create annual estimates which were then used to create the LUR model. Annual estimates followed a normal distribution with mean 16.2 and standard deviation 5.6 ppb.

A total of 55 variables were derived to characterize each sampling site by road length, vehicle density, land use, population density, elevation, longitude, latitude, distance to nearest highway, and distance from the seashore. All were considered as possible predictors of NO₂ concentrations in the final land-use regression model. Some of these predictors, such as road length and distance to highways, are coded as circular zones or “buffers” and are duplicated for

different sized buffers. Varying buffer sizes are important since they take into consideration the air pollutant dispersion patterns (5). For example, in this land-use regression model, road length, vehicle density, land use, and population density were considered buffer variables, each with buffer radii of 100, 200, 300, 500, 750, and 1,000 meters (4).

Two models were created using two different traffic metrics: road length or vehicle density. A model-building algorithm was used to create a parsimonious final model, selecting a subset of the variables to keep in the model (4). The final model equations are in Table 3-1. The R^2 values for the road length and vehicle density models were 0.56 and 0.60, respectively. Since the vehicle density model explains more variability in the data, NO_2 values were estimated using the latter model.

Table 3-1: Land-use regression model equations* using two separate traffic metrics

Model 1 (road length):	$42.6 + RD1.100 * 10.5 + RD1.1000 * 0.275 + RD2.200 * 4.24$ $+ POP.2500 * 0.074 + COM.750 * 0.116 - ELEV$ $* 0.020 - X * 0.591$
Model 2 (vehicle density):	$41.1 + AD1.100 * 0.002 + TD.200 * 0.161 + TD.1000 * 0.603$ $+ POP.2500 * 0.068 + COM.750 * 0.116 - ELEV$ $* 0.017$

* where the number after the period represents the buffer size; eg, $RD1.100$ = length of highways within a 100 m buffer. $RD1$ =length of highways, $RD2$ =length of major roads, $DIST$ =distance to highways, AD =automobile density, TD =truck density, POP =population density, $ELEV$ =elevation, X =longitude, Y =latitude, COM =commercial area, RES =residential area, IND =industrial area, and OPN =open area

The vehicle density model was rendered as a map in GIS from the regression equation above (Figure 3-1). If any NO₂ values produced from the regression equation were negative, they were set to zero. If any values were greater than the highest observed NO₂ value measured by 20%, they were reduced to an acceptable concentration. Less than 2% of values were decreased in each model.

The final land-use regression model for Vancouver was found to be relatively consistent with results from other regions, such as Montreal. The levels of NO₂ observed in Vancouver and predicted by the Vancouver LUR ranged from 0 to 30 ppb (4), while those in the Montreal study reached as high as 35.9 ppb (6). However, the coefficients for many of the final LUR model variables created for Vancouver are comparable to other models, including the Montreal LUR (6). The Montreal LUR model explained 80% of the variation in measured NO₂ in Montreal, while the Vancouver LUR explained 60% of the variation in Vancouver NO₂ (4,6). However, the effect of the complex water network surrounding the study regions of both Montreal and Vancouver may not be adequately captured by the variables generated (4).

Figure 3-1 displays the 2003 LUR model for the area of Metro Vancouver. Depicted in the figure is the province of British Columbia outside of the LUR study area (in yellow), the Pacific Ocean and waterways throughout Metro Vancouver (in blue), and the LUR model in a black-white scale. The lighter regions on the map represent higher levels of NO₂ while the darker regions represent areas of lower NO₂ exposure. Major roads and highways (the white grid lines) can also be observed due to the increased concentrations of NO₂ around these areas. The white circles are areas of commercial land-use where NO₂ concentrations are very high, hypothesized to be largely due to busy intersections and idling cars.

Figure 3-1: The 2003 NO₂ land-use regression model for Metro Vancouver

3.5.2 Back-extrapolation of the land-use regression model

The land-use regression model that was used in the second objective of this thesis project was back-extrapolated to estimate NO₂ levels in Vancouver ten years prior to study entry. Back-extrapolation of land-use regression models uses historical trends in concentrations of pollutants to estimate historical exposure to pollutants. The method used was reported in a paper by Chen et al. in 2010 (7) and is also described below.

Since women were recruited to the CBCS during 2005 to 2010, six back-extrapolated surfaces were created for the years 1995 to 2000. Regulatory fixed-site monitoring data for NO₂ concentrations were obtained for the years 1995 to 2000 from the BC Air Data Archive (<http://envistaweb.env.gov.bc.ca/>). Only monitors which were in the study area of Metro

Vancouver and had over 50% of daily measurements for the target year were used. The number of monitors used varied from 15 to 18 over the period of 1995 to 2000.

Historical estimates of NO₂ exposure were derived by multiplying the original 2003 LUR model with a ratio of inverse-distance weighted (IDW) interpolated surfaces of annual concentrations of NO₂ measured in the target year and in 2003 (Table 3-2) (7). Inverse-distance weighted interpolation was conducted in ArcGIS using an optimal power coefficient which creates a model with the lowest root mean squared error (8). An example of this surface can be seen in Figure 3-2.

Table 3-2: Formula used for back-extrapolating in time, derived from Chen et al. (7)

Method	Description of method
Original LUR ₂₀₀₃ × ratio of IDW _{fixed} [*]	$Original\ LUR_{2003} \times \frac{IDW_{observed\ [NO_2]\ for\ the\ target\ year}}{IDW_{observed\ [NO_2]\ for\ 2003}}$

* LUR: land-use regression, IDW: inverse-distance weighted interpolation, [NO₂]: concentrations of NO₂

3.5.3 Geocoding residential histories

Questionnaire data from the original Canadian Breast Cancer Study (CBCS) included information on lifetime residential histories. Participants could list up to 40 addresses and were asked for information on street address, city, postal code, country, start and termination dates in each residence, and type of residence.

Home addresses at different time points were used to estimate exposure to NO₂.

3.5.3.1 Objective 1: Time of study entry

The home address which corresponded to time of study entry for each participant was identified and geocoded using GeoPinpoint software to the region of Metro Vancouver.

Participants were excluded from this initial analysis if the address provided was missing, invalid (eg, “next door”, “downtown”), or unable to be geocoded. They were also excluded if they were not able to be assigned an NO₂ value (ie, resided outside of the LUR area), or if they were missing one or both of the years they moved to and from a given residence.

3.5.3.2 Objective 2: Ten-year latency

The home address which corresponded to ten years prior to study entry was identified and geocoded. Exclusions were made using the same criteria as in Objective 1. Due to the nature of IDW interpolation however, several participants who are within the LUR area fell outside the IDW area and were therefore excluded (Figure 3-2).

Figure 3-2: The inverse-distance weighted (IDW) interpolated surface for 1995 (marked by a red border) laid on top of the LUR model with monitors shown (yellow dots)

3.5.4 NO₂ values

Once addresses were geocoded (ie, given an x- and y-coordinate) they were mapped onto the LUR model using GIS software. NO₂ exposure values were extracted from the LUR model and assigned to each participant according to their geocoded address.

3.6 Outcome

The outcome of interest in this study is incident breast cancer. Cases were required to have an ICD code of C50 (primary breast neoplasm) that was histologically confirmed. Pathologic data was collected for all cases from the BC Cancer Registry and BC Breast Cancer Outcomes Unit. These data included tumour size, histologic type, nuclear and/or histologic

grade, presence of lymphatic or vascular invasion, estrogen and progesterone receptor (ER, PR) status, and HER2/neu protein overexpression.

3.7 Menopausal status

All analyses were stratified by menopausal status in this thesis project. The etiology of breast cancer appears to vary by menopausal status. As such, rather than include menopausal status as a confounder, these study populations will be analyzed separately. Women were classified as postmenopausal if they satisfied one of the following criteria:

- 1) they had stopped menstruating naturally for at least one year at time of diagnosis (for cases) or study entry (for controls),
- 2) they had stopped menstruating naturally and were over 50 years of age,
- 3) they had stopped menstruating and had had a bilateral oophorectomy, or
- 4) they had had a bilateral oophorectomy and were over 55 years of age.

3.8 Potential confounders

A number of established risk factors for breast cancer were identified from the literature. Data from the Canadian Breast Cancer Study questionnaire were used to obtain information on these potential confounders, including personal characteristics, reproductive health history, medical history, family history of breast cancer, and lifestyle factors (eg, oral contraceptive drug use, alcohol consumption and smoking history).

3.8.1 Demographics

Age was collected in the questionnaire as age at diagnosis for cases and age at study entry for controls. It is a continuous variable and was considered as such in all models.

There were 13 options for ethnicity: White, Chinese, South Asian, Black, Native, Arab/West Asian, Filipino, Latin American, Japanese, Korean, Southeast Asian, Other, or Mixed. Due to low numbers, some categories were collapsed, resulting in three categories: *White*, *East Asian* (Chinese, Japanese, Korean), and *Other*.

Educational history was ascertained through a question asking about the highest educational degree obtained. It was categorized into three levels: *high school or less*, *trade school certificate or community college/CEGEP*, *university degree or higher*.

Household income was categorized as *no income*; *less than \$40,000*; *\$40,000-\$59,999*; *\$60,000-\$79,999*; *over \$80,000*; and *not stated*.

3.8.2 Reproductive, medical, and family history

Information on aspects of reproductive history (age at menarche, age at first full-term pregnancy, nulliparity, number of pregnancies, duration of breastfeeding, and age at bilateral oophorectomy) was collected in the questionnaire. These were all considered established risk factors with the exception of breastfeeding and younger age (< 35 years) at bilateral oophorectomy which are protective factors (9). However, age at bilateral oophorectomy was not applicable in the models for premenopausal breast cancer and, it was only controlled for in the fully-adjusted model for postmenopausal women.

Medical factors included hormonal prescriptive drug use and BMI. Oral contraceptive (OC) use and hormone replacement therapy (HRT) use were categorized into *never used* and *used*. Self-reported height and weight were used to calculate body-mass index (BMI), calculated as body weight in kilograms over height in meters squared. Self-reported heights and weights are often over- and underestimated, respectively, in women, so calculated BMI values are likely an underrepresentation of the real values (10).

Family history of breast cancer is captured in the questionnaire by asking participants to list all first-degree relatives (mother, sister, daughter) with breast cancer. This was coded as a yes/no variable (ie, “yes, I have at least one first degree relative with breast cancer”, vs. “no, I have none”).

3.8.3 Lifestyle factors

Various lifestyle factors (alcohol consumption, smoking status, and pack-years smoked) were identified as risk factors for breast cancer and potential confounders. Participants were asked to fill out a table in the CBCS questionnaire describing the average number of alcoholic drinks (beer, wine, and spirits recorded separately) consumed per day or per week in each decade of their lives (eg, 20s, 30s, 40s, 50s). Alcohol consumption was summarized as average number of drinks consumed per week in the decade corresponding to the participant’s age.

Smoking status was characterized as *never smoked*, *former smoker*, and *current smoker*. If a participant smoked less than 100 cigarettes in their lifetime, they were categorized as a never-smoker. Pack-years were calculated as number of packs smoked (20 cigarettes per pack) per day for the total years smoked.

3.8.4 Neighbourhood-level factors

Additionally, two neighbourhood-level variables were considered as potential confounders to control for potential neighbourhood effects. A neighbourhood effect can be defined as the effect that the characteristics of a neighbourhood may have on the resident's health beyond the individual lifestyles of the residents (11) and may have an effect on health independent of the same individual-level factors(12). Neighbourhood effects can encompass service environments (eg, medical care and transportation), social environments (eg, social support, crime), and physical environments (eg, the built environment, traffic, crowding) (11,12). Data from the 2006 and 1996 census were used to generate the two neighbourhood-level covariates at the census-tract level: proportion of adults over the age of 25 with at least a high school education and median household income. Neighbourhood-level median household income was categorized similarly to individual-level household income.

3.9 Statistical analyses

3.9.1 Main objectives

Descriptive statistics were conducted for the exposure variable as well as all covariates for cases and controls. To determine if variables should be categorized or kept continuous, Goodness-of-fit tests and AIC (Akaike information criterion) were used. Age at first live birth, age at bilateral oophorectomy, duration of breastfeeding, oral contraceptive and hormone replacement therapy use were categorized from continuous variables. Means and standard deviations were calculated for continuous variables and frequency tables were generated for categorical variables. T-tests and chi-square tests (Fisher's exact tests, when appropriate) were

conducted to test the differences between cases and controls for continuous and categorical variables, respectively. Age-adjusted odds ratios for established and suspected risk factors were also calculated, adjusting for age.

Multivariable logistic regression was used to estimate the independent relationship between exposure to NO₂ and risk of breast cancer. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the logistic regression models and are considered a reasonable estimate of the relative risk. Since cases and controls were frequency-matched by age, the age variable was forced into each model. Models were created for the objectives outlined above. Using goodness-of-fit tests (Hosmer-Lemeshow and Stukel's tests), it was confirmed that the linearity assumptions of logistic regression have not been violated.

A fully-adjusted model was generated by adjusting for all covariates that were considered risk factors identified from the literature.

3.9.2 Sensitivity analyses

Additional sensitivity analyses were conducted:

3.9.2.1 Exclusion of cases with diagnosis dates greater than two years from study entry

In this sensitivity analysis, cases that were diagnosed two years or more before study entry were excluded. This analysis was conducted to minimize incidence-prevalence bias and to assess the relationship between NO₂ exposure and breast cancer for cases with more incident diagnoses of breast cancer.

3.9.2.2 Exclusion of participants with more than one residence in the ten years prior to study entry

This sensitivity analysis was limited to participants who had lived at the same address for greater than ten years prior to study entry. It is possible for participants to have moved outside the Vancouver region or from an area of high pollution to low pollution in the years prior to study entry. By limiting participants to those with one long-time address, misclassification due to frequent moving is minimized.

3.9.2.3 Exclusion of cases who have never attended screening mammography

Cases who had never participated in screening mammography were excluded in this sensitivity analysis. This analysis was performed to minimize the potential bias that recruiting controls from a screening mammography program might have introduced. Cases were linked to the Screening Mammography Program of BC with their provincial personal health numbers. Those that were not found in the program were excluded.

3.9.2.4 Exclusion of participants who were not born in Canada

Participants who were not born in Canada were excluded in this sensitivity analysis. Information was also collected on place of birth, which was considered a proxy for immigrant status. This was coded as a yes/no variable (ie, born in Canada or not). Vancouver is home to many immigrants and in 1996, 35% of the population were immigrants, which rose to 37.5% in 2001 and 40% in 2006) (13). Despite the data to suggest that first generation immigrants

typically come from a lower SES background, they are also more likely to be in better health or more health-conscious than their Canadian-born counterparts (eg, a native Canadian aged 45 years has a 55% predicted incidence of a non-life threatening disease such as asthma compared to a recent immigrant, whose predicted incidence is less than 30%) (14). This is known as the “healthy immigrant effect” and has been observed in Canadian and American populations (14,15) which may introduce bias into effect estimates. This effect may be attributable to the fact that healthier candidates for immigration may be more financially or physically capable of immigrating or are more likely to be eligible for Canadian residency based on health screening by Canadian officials (14).

3.9.2.5 Exclusion of participants who never attended screening mammography and who were not born in Canada

In this analysis, for the reasons outlined above in sections 3.9.2.3 and 3.9.2.4, this analysis will exclude cases who had never attended screening mammography as well as participants who were not born in Canada.

3.9.3 Power

Power was calculated for several logistic regression analyses in a case-control setting with no confounder adjustment, using methods described by Lubin et al. (16). Based on the results reported in the Montreal case-control study in which the largest significant effect estimate observed was 1.3 per 5 ppb increases in NO₂, (17), a minimal clinically significant odds ratio of 1.3 per 5 ppb increases was selected for this project’s original power calculation. The distribution

of the exposure (NO₂ in Vancouver) was taken from the observed monitor measurements of NO₂ reported in the LUR methods paper: they were normally distributed with a mean of 16.2 ppb and a standard deviation of 5.6 ppb (4). Table 3-3 displays the power for the analyses conducted in this thesis using the sample sizes for each objective.

Table 3-3: Power calculations

Population	Cases	Controls	Power
Objective 1			
Postmenopausal women	617	579	99.99%
Premenopausal women	345	366	98.79%
Objective 2			
Postmenopausal women	421	382	99.37%
Premenopausal women	212	236	92.55%

3.10 References

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Chapter 4

Results

4.1 Objective 1: Cross-sectional analysis

The first objective for this thesis was to assess the association between NO₂ exposure at study entry and risk of breast cancer. NO₂ estimates were derived for each participant based on her home address at time of study entry for both cases (as a proxy for diagnosis date) and controls.

4.1.1 Residential histories

Cases and controls each listed an average of 5.2 residences with information at the street level; the most any participant gave was 20 residences. On average, participants lived at their last given street address for 13.9 years (13.6 years for cases and 14.1 years for controls) and listed street addresses for 39.2 years (38.6 years for cases and 39.7 years for controls). There appears to be no evidence of recall bias of residential history by disease status. A breakdown of the proportion of women with 0 to 13 street addresses in the ten, 20, and 30 years before study entry are shown in Table 4-1.

A total of 2,015 participants were found to be eligible from the original Canadian Breast Cancer Study. Out of these eligible participants, the only exclusion criterion for these analyses was not having a valid street address that could be geocoded within the land-use regression (LUR) model. One-hundred and six participants (37 cases and 69 controls) were excluded due to the reasons outlined in Table 4-2, resulting in a final sample size of 1,909 participants (964 cases and 945 controls).

Table 4-1: Number of cases and controls with varying number of street addresses in 10, 20, and 30 years before study entry in the original study population (1,001 cases and 1,014 controls)

# addresses	10 years before study entry		20 years before study entry		30 years before study entry	
	Cases	Controls	Cases	Controls	Cases	Controls
0	37	66	37	61	32	54
1	579	576	314	327	203	202
2	245	260	291	264	243	212
3	101	83	158	176	160	186
4-5	45	28	161	143	211	215
6-8	3	3	49	43	130	121
9-11	0	0	0	2	28	23
12-13	0	0	0	0	3	3

Table 4-2: Frequency table of reasons for excluded cases and controls for objective 1

Cases (%) N=1,001	Controls (%) N=1,014	Reason
14 (1.4)	6 (0.6)	Had no residential information for the target year
15 (1.5)	47 (4.6)	Not enough information given in address
1 (0.1)	2 (0.2)	Address was outside Canada (eg, Washington)
1 (0.1)	6 (0.6)	Invalid addresses (eg, “4 addresses”, “next door”)
1 (0.1)	4 (0.4)	Could not confirm address for target year

4 (0.4)	5 (0.5)	No address existed for the target year
1 (0.1)	7 (0.7)	Within Canada but outside the LUR region
Total: 37 (3.7)		Total: 69 (6.8)

4.1.2 NO₂

Table 4-3 shows NO₂ concentrations for premenopausal and postmenopausal women. On average, premenopausal women were exposed to more NO₂ than postmenopausal women. Cases had more variable NO₂ exposures (higher standard deviation) than controls. In both groups, cases and controls did not differ significantly in their average NO₂ exposures (p-value=0.751 and 0.160 for postmenopausal and premenopausal women respectively).

A higher proportion of cases and controls (5.5% of cases and 3.4% of controls) were assigned the maximum NO₂ exposure of 30 ppb (in the cross-sectional analyses) than would be expected from a normally distributed exposure (Henderson et al. observed measurements of NO₂ from the monitoring stations were normally distributed with a mean of 16.2 ppb and a standard deviation of 5.6 ppb (1)). As such, the median exposure concentration is lower than the mean for both groups of cases and controls in this project.

Table 4-3: Average NO₂ levels in parts-per-billion (ppb) for post- and premenopausal women

Postmenopausal women			
NO ₂ (ppb)	Cases (N=617)	Controls (N=579)	p-value*
Mean (SD)	18.4 (4.2)	18.3 (3.9)	0.751

Median	17.3	17.3	
Premenopausal women			
NO₂ (ppb)	Cases (N=345)	Controls (N=366)	p-value*
Mean (SD)	18.2 (4.2)	17.8 (3.6)	0.160
Median	17.2	17.3	

* p-values were calculated for two independent sample t-tests

4.1.3 Descriptive statistics

Characteristics of cases and controls are described in Table 4-4 by menopausal status. Two cases were excluded due to missing information on menopausal status. In both postmenopausal and premenopausal women, significant differences between cases and controls were observed for ethnicity, education, and household income. There was a higher proportion of Asians and a smaller proportion of whites among cases when compared to controls. Controls in both groups were more educated and wealthier. In terms of reproductive factors, in both groups, cases and controls did not differ in mean age at menarche or hormone replacement therapy use. In postmenopausal women only, differences between cases and controls in number of first-degree relatives with breast cancer, age at first birth, and duration of breastfeeding were significant. Cases were more likely to have given birth before the age of 22 while controls were more likely to have never given birth. Controls also breastfed for a longer duration (p-value=0.05). Premenopausal controls were more likely to have no children. While in both groups, there were no differences in smoking status or pack-years smoked, controls were more

likely to have used oral contraceptives and drank more alcohol. Postmenopausal cases had a significantly higher BMI than controls; this difference was not seen in premenopausal women.

Bivariate analyses were also conducted for each of the covariates and risk of breast cancer for postmenopausal women and premenopausal women (see Appendix C, Table C-1). Similar relative risks (increased or decreased) for breast cancer were seen for each sample of women for each covariate, except in the case of BMI. Higher BMI was associated with a significant increased risk for breast cancer in the postmenopausal sample, but was associated with a decreased risk (although not significant) in the premenopausal sample. In some classic risk factors, the direction of risk was the opposite of expected (ie, instead of protective, it was a risk factor). This is the case for ethnicity, education, household income, age at menarche, OC and HRT use, and alcohol consumption. All odds ratios other than BMI followed the same direction of risk or protection for postmenopausal and premenopausal women.

Table 4-4: Characteristics of the study population for postmenopausal and premenopausal women for all covariates by case and control status

	POSTMENOPAUSAL WOMEN			PREMENOPAUSAL WOMEN		
CHARACTERISTICS	CASES	CONTROLS	p-value*	CASES	CONTROLS	p-value*
	(n=617) [Mean (SD)/N (%)]	(n=579) [Mean (SD)/N (%)]		(n=345) [Mean (SD)/N (%)]	(n=366) [Mean (SD)/N (%)]	
AGE	62.2 (8.2)	62.3 (8.1)	0.799	46.4 (3.9)	46.8 (3.8)	0.224
ETHNICITY						
White	377 (61.1)	456 (78.8)	<.0001	175 (50.7)	246 (67.2)	<.0001
East Asian	147 (23.8)	62 (10.7)		119 (34.5)	68 (18.6)	
Other	93 (15.1)	61 (10.5)		51 (14.8)	52 (4.2)	
EDUCATION, highest level achieved						
High school or less	253 (41.5)	169 (29.2)	<.0001	76 (22.0)	56 (15.3)	0.022
Trade certificate/Completed community college/CEGEP	171 (28.0)	166 (28.7)		110 (31.9)	107 (29.3)	
University, graduate, or professional degree	186 (30.5)	243 (42.0)		159 (46.1)	202 (55.4)	
Missing	7	1		0	1	
HOUSEHOLD INCOME						
< \$40,000	121 (19.9)	62 (10.8)	<.0001	61 (18.3)	34 (9.3)	0.001

CHARACTERISTICS	POSTMENOPAUSAL WOMEN			PREMENOPAUSAL WOMEN		
	CASES	CONTROLS	p-value*	CASES	CONTROLS	p-value*
	(n=617) [Mean (SD)/N (%)]	(n=579) [Mean (SD)/N (%)]		(n=345) [Mean (SD)/N (%)]	(n=366) [Mean (SD)/N (%)]	
\$40,000 to \$59,999	156 (25.6)	136 (23.7)		74 (22.2)	70 (19.1)	
\$60,000 to \$79,999	69 (11.3)	72 (12.5)		37 (11.1)	49 (13.4)	
\$80,000 to $\geq$ \$100,000	52 (8.6)	49 (8.5)		38 (11.4)	43 (11.7)	
No income	105 (17.2)	91 (15.8)		22 (6.6)	49 (13.4)	
Not stated	106 (17.4)	165 (28.7)		101 (30.4)	121 (33.1)	
Missing	8	4		12	0	
# FIRST-DEGREE RELATIVES WITH BREAST CANCER						
None	488 (79.1)	499 (86.2)	0.001	287 (83.2)	321 (87.7)	0.087
At least one	129 (20.9)	80 (13.8)		58 (16.8)	45 (12.3)	
AGE AT MENARCHE	13.0 (1.7)	12.9 (1.5)	0.098	12.7 (1.4)	12.8 (1.5)	0.548
Missing	5	5		1	3	
AGE AT FIRST BIRTH						
Never pregnant	96 (15.6)	105 (18.1)	0.353	67 (19.4)	100 (27.4)	0.035
< 29	300 (48.7)	261 (45.1)		86 (24.9)	89 (24.4)	
$\geq$ 29	220 (25.7)	213 (36.8)		192 (55.7)	176 (48.2)	

CHARACTERISTICS	POSTMENOPAUSAL WOMEN			PREMENOPAUSAL WOMEN		
	CASES	CONTROLS	p-value*	CASES	CONTROLS	p-value*
	(n=617) [Mean (SD)/N (%)]	(n=579) [Mean (SD)/N (%)]		(n=345) [Mean (SD)/N (%)]	(n=366) [Mean (SD)/N (%)]	
Missing	1	0		0	1	
# OF PREGNANCIES						
0	97 (15.7)	105 (18.1)	0.114	67 (19.4)	101 (27.6)	0.026
< 2	84 (13.6)	58 (10.0)		64 (18.6)	53 (14.5)	
≥ 2	436 (70.7)	416 (71.8)		214 (62.0)	212 (57.9)	
DURATION OF BREASTFEEDING, months						
< 12	487 (78.9)	426 (73.6)	0.050	255 (73.9)	248 (67.8)	0.161
12 to < 24	73 (11.8)	96 (16.6)		58 (16.8)	81 (22.1)	
≥ 24	57 (9.2)	57 (9.8)		32 (9.3)	37 (10.1)	
AGE AT BILATERAL OOPHORECTOMY						
Never had	555 (90.0)	515 (89.0)	0.948	N/A	N/A	N/A
< 40	10 (1.6)	10 (1.7)		N/A	N/A	
40 to < 50	25 (4.0)	25 (4.3)		N/A	N/A	
≥ 50	27 (4.4)	29 (5.0)		N/A	N/A	
OC USE						

CHARACTERISTICS	POSTMENOPAUSAL WOMEN			PREMENOPAUSAL WOMEN		
	CASES	CONTROLS	p-value*	CASES	CONTROLS	p-value*
	(n=617) [Mean (SD)/N (%)]	(n=579) [Mean (SD)/N (%)]		(n=345) [Mean (SD)/N (%)]	(n=366) [Mean (SD)/N (%)]	
Never used	281 (45.5)	221 (38.2)	0.007	153 (44.5)	92 (25.1)	<.0001
Used	332 (54.2)	358 (61.8)		191 (55.5)	274 (74.9)	
Missing	4	0				
HRT USE						
Never used	339 (55.0)	207 (53.0)	0.486	328 (95.3)	342 (93.7)	0.335
Used	277 (45.0)	272 (47.0)		16 (4.7)	23 (6.3)	
Missing	1	0		1	1	
AVERAGE ALCOHOL CONSUMPTION, drinks/week based on age						
	3.9 (2.9)	5.0 (2.8)	<.0001	4.2 (3.0)	5.3 (2.8)	<.0001
SMOKING STATUS						
Non-smoker	362 (58.7)	327 (56.5)	0.744	232 (67.3)	232 (63.4)	0.505
Former	213 (34.5)	211 (36.4)		96 (27.8)	111 (30.3)	
Current	42 (6.8)	41 (7.1)		17 (4.9)	23 (6.3)	
AVERAGE LIFETIME PACKYEARS						
	7.2 (14.4)	6.3 (12.6)	0.266	3.4 (7.7)	2.9 (6.5)	0.371
Missing	1	0		1	0	

CHARACTERISTICS	POSTMENOPAUSAL WOMEN			PREMENOPAUSAL WOMEN		
	CASES	CONTROLS	p- value*	CASES	CONTROLS	p- value*
	(n=617)	(n=579)		(n=345)	(n=366)	
	[Mean (SD)/N (%)]	[Mean (SD)/N (%)]		[Mean (SD)/N (%)]	[Mean (SD)/N (%)]	
BMI, kg/m ²	26.2 (5.7)	25.0 (4.6)	<.0001	24.1 (4.9)	24.5 (4.9)	0.282
Missing	5	7		6	4	

* p-values were calculated for two independent sample t-tests

4.1.4 Association between NO₂ and breast cancer

Two models were conducted for assessing the association between continuous NO₂ (per 5 ppb increases) and breast cancer: age-adjusted and fully-adjusted (Table 4-5). Additional participants were excluded from the fully-adjusted models due to missing data for the covariates (29 cases and 21 controls in the postmenopausal sample; 21 cases and 10 controls in the premenopausal sample).

In postmenopausal women only, the fully-adjusted OR_{5ppb} was 0.96 (95% CI: 0.81, 1.14) while in premenopausal women, the fully-adjusted OR_{5ppb} was 1.17 (95% CI: 0.93, 1.48).

Table 4-5: Age-adjusted and fully-adjusted models for association between NO₂ exposure and breast cancer with odds ratios per 5 ppb increases in NO₂ (OR_{5ppb})

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	617	579	1.03 (0.89, 1.18)	588	558	0.96 (0.81, 1.14)
Premenopausal[‡]	345	366	1.15 (0.95, 1.39)	324	356	1.17 (0.93, 1.48)

[†] adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

‡ age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.2 Objective 2: Historical analysis

The second objective of this thesis was to analyze the association between historical NO₂ exposures from ten years before study entry and breast cancer risk. The association was assessed stratified by menopausal status, similar to the analyses in the first objective.

4.2.1 Residential histories

A total of 763 participants (366 cases and 396 controls) were excluded from this analysis from the original sample of 2,015 eligible participants. Due to the nature of this “historical” analysis, which was to assign NO₂ estimates to participants ten years prior to study entry based on a back-extrapolation approach, many participants were excluded because of missing data (addresses or move years) or not living in the study area ten years ago. Additionally, approximately half of the excluded participants resided outside of the inverse-distance weighted (IDW) interpolated surfaces used in the back-extrapolation methods, which resulted in no available NO₂ estimates. Table 4-6 outlines the different reasons why participants were excluded.

Table 4-6: Frequency table of excluded cases and controls with reasons for objective 2

Cases (%) N=1,001	Controls (%) N=1,014	Reason
152 (15.2)	181 (1.8)	Outside the IDW region

12 (1.2)	8 (0.8)	Not enough information given in address
64 (6.4)	86 (8.5)	Missing address for target year
12 (1.2)	18 (1.8)	Invalid addresses (eg, “4 addresses”, “next door”)
5 (0.5)	11 (1.1)	Could not confirm address for target year
122 (1.2)	92 (9.1)	Outside the LUR region
<hr/>		
Total: 366 (36.6)	Total: 396 (39.0)	
<hr/>		

4.2.2 NO₂

Historical NO₂ exposures did not differ significantly between cases and controls in the postmenopausal women sample (p-value=0.646) or in the premenopausal women sample (p-value=0.557). Similar to the cross-sectional analysis, median values for NO₂ were lower than the means (Table 4-7).

Table 4-7: NO₂ means, standard deviations, and medians in parts-per-billion (ppb) for post- and premenopausal women

Postmenopausal women			
NO₂	Cases (N=421)	Controls (N=382)	p-value*
Mean (SD)	19.2 (4.4)	19.3 (4.2)	0.646
Median	18.1	18.5	
Premenopausal women			
NO₂	Cases (N=212)	Controls (N=236)	p-value*

Mean (SD)	19.1 (4.7)	19.4 (4.4)	0.557
Median	18.1	18.7	

* p-values were calculated for two independent sample t-tests

4.2.3 Association between NO₂ and breast cancer

The same models were created in this objective as with the first: age-adjusted and fully-adjusted for all *a priori* identified covariates. Effect estimates (odds ratios, calculated as the relative odds of having breast cancer for a 5 ppb increase in NO₂ with all else being equal) from the age-adjusted and fully-adjusted models were not statistically significant since all confidence intervals include the null value of one (Table 4-8). However, a similar pattern is observed: in postmenopausal women only, the fully-adjusted OR_{5ppb} was 0.93 (95% CI: 0.78, 1.11) while in premenopausal women, the fully-adjusted OR_{5ppb} was stronger: 1.18 (95% CI: 0.93, 1.49).

Table 4-8: Age-adjusted and fully-adjusted models for association between NO₂ exposure and breast cancer with odds ratios per 5 ppb increases in NO₂ (OR_{5ppb})

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	421	382	0.97 (0.82, 1.14)	402	368	0.93 (0.78, 1.11)
Premenopausal[‡]	212	236	0.94 (0.76, 1.15)	203	230	1.18 (0.93, 1.49)

† adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

‡ age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.3 Sensitivity analyses

Several sensitivity analyses were conducted to evaluate certain assumptions that were made. They are described in more detail in the following section.

4.3.1 Exclusion of cases with diagnosis dates greater than two years from study entry

This sensitivity analysis was restricted to cases whose diagnosis date was less than two years from study entry, to better represent incident breast cancer cases. All originally eligible controls for each main analysis (exposure estimated at the time of study entry and ten years prior using back-extrapolation) were included. The restrictions for this sensitivity analysis led to the further exclusion of 84 cases from the cross-sectional analysis and 52 cases from the back-extrapolation analysis. Compared to the original analyses, effect estimates did not change substantially and all results remain null (Table 4-9).

Table 4-9: Age-adjusted and fully-adjusted logistic regression models excluding cases with diagnosis dates greater than two years from study entry using NO₂ estimates at study entry (Table 4-9A) and back-extrapolated historical NO₂ estimates (Table 4-9B)

Table 4-9A: (Cross-sectional)

	Age-adjusted			Fully-adjusted[†]		
	Cases	Controls	OR_{5ppb} (95% CI)	Cases	Controls	OR_{5ppb} (95% CI)
Postmenopausal	570	579	1.03 (0.89, 1.19)	543	558	0.98 (0.82, 1.16)
Premenopausal[†]	308	366	1.14 (0.93, 1.38)	289	356	1.16 (0.91, 1.47)

Table 4-9B: (Historical)

	Age-adjusted			Fully-adjusted[†]		
	Cases	Controls	OR_{5ppb} (95% CI)	Cases	Controls	OR_{5ppb} (95% CI)
Postmenopausal	392	382	0.99 (0.84, 1.16)	373	368	0.95 (0.79, 1.14)
Premenopausal[†]	189	236	0.94 (0.76, 1.16)	181	230	1.06 (0.82, 1.34)

[†] adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

‡ age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.3.2 Exclusion of participants with more than one residence in the ten years prior to study entry

The second sensitivity analysis conducted excluded participants who moved during a period of ten years prior to their year of study entry. This was to reduce any misclassification from having an individual with several residences being assigned an exposure from only one residence. Due to the nature of the back-extrapolation method, participants who fell outside of the IDW surfaces were excluded. For the cross-sectional analysis, 348 cases and 320 controls were excluded, while for the historical analysis, 140 cases and 129 controls were excluded. Similar to the first sensitivity analysis, effect estimates do not differ greatly from the original analyses and are not statistically significant (Table 4-10). An elevated odds ratio can be observed in the cross-sectional analysis using premenopausal women ($OR_{5ppb}=1.21$, 95% CI: 0.84, 1.76).

Table 4-10: Age-adjusted and fully-adjusted logistic regression models excluding participants with more than one address in the ten years from study entry using NO₂ estimates at study entry (Table 4.10A) and back-extrapolated historical NO₂ estimates (Table 4.10B)

Table 4.10A: (Cross-sectional)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	449	447	1.04 (0.87, 1.23)	428	434	0.94 (0.77, 1.16)
Premenopausal[‡]	165	178	1.04 (0.78, 1.40)	154	174	1.21 (0.84, 1.76)

Table 4.10B: (Historical)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	363	340	1.01 (0.85, 1.20)	345	329	1.00 (0.82, 1.22)
Premenopausal[‡]	130	149	0.93 (0.70, 1.23)	124	144	1.09 (0.77, 1.55)

[†] adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

[‡] age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.3.3 Exclusion of cases who have never attended screening mammography

In this third sensitivity analysis, to assess the possibility of screening-related bias due to the selection strategy of the controls, cases who had never attended screening mammography were excluded. A total of 213 cases from the cross-sectional analysis and 126 cases from the back-extrapolation analyses were excluded. The same pattern persisted in the cross-sectional analysis with a weak but not statistically significant association observed in the premenopausal sample only. This association increased moderately in the historical model, but again, was not statistically significant (Table 4-11).

Table 4-11: Age-adjusted and fully-adjusted logistic regression models excluding cases who have never attended screening mammography using NO₂ estimates at study entry (Table 4.11A) and back-extrapolated historical NO₂ estimates (Table 4.11B)

Table 4.11A: (Cross-sectional)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	534	579	1.03 (0.89, 1.19)	508	558	0.99 (0.83, 1.18)
Premenopausal[‡]	215	366	1.10 (0.89, 1.37)	202	356	1.12 (0.86, 1.47)

Table 4.11B: (Historical)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	377	382	0.99 (0.84, 1.16)	359	368	0.98 (0.81, 1.18)
Premenopausal[‡]	130	236	0.99 (0.79, 1.25)	124	230	1.20 (0.91, 1.59)

[†] adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

[‡] age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.3.4 Exclusion of participants who were not born in Canada

Participants who were not born in Canada were excluded in this sensitivity analysis to assess for a possible healthy immigrant effect (2,3). For the first analysis, 539 cases and 394 controls were excluded. For the second analysis, 342 cases and 242 controls were excluded. The pattern of results was similar to previous models with a weak but not statistically significant association observed predominantly in the premenopausal analyses. Since many participants were excluded in this analysis, confidence intervals are wider than in previous analyses and all include the null value of one (Table 4-12).

Table 4-12: Age-adjusted and fully-adjusted logistic regression models excluding participants not born in Canada using NO₂ estimates at study entry (Table 4.12A) and back-extrapolated historical NO₂ estimates (Table 4.12B)

Table 4.12A: (Cross-sectional)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	279	331	1.01 (0.82, 1.25)	267	321	0.95 (0.73, 1.22)
Premenopausal[†]	144	220	1.13 (0.82, 1.56)	135	216	1.23 (0.82, 1.86)

Table 4.12B: (Historical)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	194	214	0.98 (0.77, 1.23)	188	208	1.05 (0.81, 1.38)
Premenopausal[†]	97	162	0.94 (0.70, 1.25)	93	158	1.08 (0.76, 1.52)

[†] adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

‡ age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.3.5 Exclusion of participants who have never attended screening mammography and who were not born in Canada

Cases who had never attended screening mammography were excluded to assess the possibility of screening-related bias due to the selection strategy of the controls. In addition, participants who were not born in Canada were excluded in this sensitivity analysis to assess for a possible healthy immigrant effect (2,3). While all confidence intervals include the null value of one, effect estimates seen in this analysis are stronger than observed in previous analyses, particularly in the premenopausal sample (Table 4-13).

Table 4-13: Age-adjusted and fully-adjusted logistic regression models excluding participants who have never attended screening mammography and who were not born in Canada using NO₂ estimates at study entry (Table 4.13A) and back-extrapolated historical NO₂ estimates (Table 4.13B)

Table 4.13A: (Cross-sectional)

	Age-adjusted			Fully-adjusted [†]		
	Cases	Controls	OR _{5ppb} (95% CI)	Cases	Controls	OR _{5ppb} (95% CI)
Postmenopausal	252	331	1.04 (0.84, 1.28)	239	321	0.99 (0.77, 1.29)

Premenopausal[‡]	101	220	1.08 (0.74, 1.58)	94	215	1.22 (0.76, 1.94)
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Table 4.13B: (Historical)

	Age-adjusted			Fully-adjusted[†]		
	Cases	Controls	OR_{5ppb} (95% CI)	Cases	Controls	OR_{5ppb} (95% CI)
Postmenopausal	176	214	1.02 (0.80, 1.29)	169	208	1.15 (0.87, 1.51)
Premenopausal[‡]	64	162	1.07 (0.77, 1.48)	61	158	1.37 (0.92, 2.05)

[†] adjusted for age, family history of breast cancer, education, ethnicity, age at menarche, age at first live birth, parity, breastfeeding duration, age at bilateral oophorectomy, oral contraceptive use, hormone replacement therapy use, body-mass index, smoking status, pack-years smoked, average alcohol consumption, and two neighbourhood-level variables, proportion of adults with at least high school education and median household income

[‡] age at bilateral oophorectomy could not be adjusted for in the premenopausal sample

4.4 References

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Chapter 5

Discussion

5.1 Summary of main findings

This study found limited evidence of an association between exposure to outdoor concentrations of NO₂ and incidence of breast cancer in a case-control study conducted between 2005 and 2010 in Vancouver, BC. Two exposure metrics were used to determine concentrations of NO₂: cross-sectional concentrations taken at time of entry into the case-control study (between the years 2005 and 2010), and historical concentrations taken ten years prior to study entry (between 1995 and 2000).

Specifically, the analysis at study entry included 964 cases and 945 controls and used local NO₂ estimates from a 2003 land-use regression (LUR) model developed for the city of Vancouver and its surrounding areas. The average concentration of NO₂ was approximately 18 ppb for both cases and controls, but was not normally distributed, likely due to the truncation of the LUR model at a maximum exposure of 30 ppb. The original Vancouver LUR methods paper reported measurements of NO₂ from the passive monitoring stations to be normally distributed (1), but the estimates for participants in this thesis project were not. No association between NO₂ exposure (per 5 ppb increases) and risk of breast cancer incidence was observed in the postmenopausal sample of women (OR_{5ppb}=0.96, 95% CI: 0.81, 1.14 for the cross-sectional analysis and OR_{5ppb}=0.93, 95% CI: 0.78, 1.11 for the historical analysis). A consistent positive association between NO₂ exposure and incidence of breast cancer in premenopausal women was observed, although the odds ratios never reached statistical significance at the conventional alpha level of 0.05 (OR_{5ppb}=1.17, 95% CI: 0.93, 1.48 for the cross-sectional analysis and OR_{5ppb}=1.18,

95% CI: 0.93, 1.49 for the historical analysis). When the analysis was restricted to only premenopausal cases and controls that had attended mammography screening, the magnitude of the association between historical exposure to NO₂ and incidence of breast cancer increased, although the confidence interval still included one (OR_{5ppb}=1.20; 95% CI 0.91, 1.59).

The remainder of this chapter will compare the results from this project with the current literature on traffic-related air pollution and incidence of breast cancer. The methodological strengths and limitations of this research are presented including suggestions for future research directions.

5.2 Comparison of findings with relevant literature

To date, there have been only a handful of studies evaluating the association between traffic-related air pollution and breast cancer (2-7). Of these, two used traffic exposure metrics (3,4), one measured total suspended particulates (5), and three used measurements of NO_x (2,6,7) to estimate exposure to traffic-related air pollution. Results from some of these studies are provocative, suggesting weak to modest associations between different markers of air pollution and incidence of breast cancer, although the majority of observed effect estimates have not been statistically significant at the alpha level of 0.05. There also appears to be qualitative heterogeneity by menopausal status in the literature and results seem to vary according to study design and exposure assessment strategy.

Similar to the results observed in this study, a recent publication by Hystad and colleagues observed an increased incidence in premenopausal breast cancer (OR=1.28, 95% CI: 0.92, 1.79, per 10 ppb increases in NO₂) among women with an elevated exposure to NO₂ (based

on a 20 year average) but a weak to negligible association between increased exposure to NO₂ and incidence of postmenopausal breast cancer (OR=1.07, 95% CI: 0.86, 1.32, per 10 ppb increases in NO₂) (6). Like this project, Hystad et al. also used data from a case-control study and estimated NO₂ using a LUR approach. In contrast, the only other study in Canada to use a LUR approach to estimate NO₂ exposure, conducted by Crouse et al., observed a much stronger association between increased NO₂ exposure (per 5 ppb increases) and risk of postmenopausal breast cancer (OR_{5ppb}=1.31; 95% CI: 1.00, 1.71) (7). Crouse and collaborators used city-level data from Montreal for NO₂ exposure assignment, finer resolution than the national-level data used in the Hystad study, and this difference in precision in exposure assessment may explain the difference in their results. However, it does not explain the difference observed between the Montreal study and this thesis project that also used city-level data but did not observe an association between NO₂ and risk of breast cancer among postmenopausal women.

A few other studies in predominantly postmenopausal populations, albeit using different markers of exposure to traffic-related air pollution, have also reported elevated risk of breast cancer with increased exposure to air pollution. In these studies, the direction of the effect has been consistently positive (2,3,5), although only one of the three studies (5) observed a statistically significant result. Furthermore, the study by Lewis-Michl also observed an inverse association between traffic density and breast cancer among postmenopausal women in Suffolk County (OR=0.89, 95% CI: 0.40, 1.99) in contrast to those living in Nassau County (OR=1.29, 95% CI: 0.77, 2.15) (3). The authors hypothesized that the higher probability of greater exposure in Nassau country than in Suffolk and the difference in case participation rates in each county may be reasons why this difference was observed.

There are several explanations for the discrepancy in effect estimates for postmenopausal women in this project and those reported elsewhere in the literature. The Montreal study (7) used two methods to back-extrapolate the NO₂ LUR models: the first method, also used in this thesis, used fixed-site monitoring station NO₂ measurements to create inverse-distance weighted interpolation maps for the target years and year of LUR creation, while the second method used predicted NO₂ values from the 2005 LUR model at the locations of the fixed-site monitoring stations (8). Both methods produced very similar estimates of effects (7) for the time periods of interest (time of study entry: 1996; time of LUR development: 2006; and historical exposure ten years prior: 1986), although only the second back-extrapolation procedure for the 1996 (cross-sectional) model produced results that were statistically significant. In this thesis project, back-extrapolation of NO₂ estimates based on an LUR model developed in 2003 did not change the magnitude of the estimated association except perhaps in two analyses restricted to 1) prior participation in a screening mammography program and 2) participants born in Canada. In both of these sub-analyses, increased exposure to NO₂ was associated with an elevated risk of breast cancer among premenopausal women. When restricted to postmenopausal participants born in Canada, the OR_{5ppb} of 1.08 (95% CI: 0.76, 1.52) compared most closely to the results from Hystad et al. (OR_{10ppb}=1.07, 95% CI: 0.86, 1.32) (6). It is possible that while an effect may exist between NO₂ and postmenopausal breast cancer, the study in Vancouver did not have enough statistical power to detect this association. For example, if the true relationship between NO₂ and breast cancer was non-linear and associations are only apparent after a certain threshold, the city of Vancouver may not have the correct prevalence of high exposures to NO₂ to detect them. Importantly, NO₂ estimates from the LUR model were restricted to a maximum threshold of 30 ppb in the Vancouver LUR model. It cannot be explained why this might have differentially

affected the results by menopausal status. In addition, although this study initially reported high power to detect an association of 1.3 under the assumption of a normally distributed exposure (see Section 3.9), this assumption may not be valid and the effects of a non-normally distributed exposure on the power calculated is not known.

Some study limitations and different methodological approaches may account for observed differences between studies. One limitation is the fundamentally different air quality between Montreal, Vancouver, and other major Canadian cities which influences NO₂ variability and exposure levels. For example, Montreal has a larger population, almost double that of Vancouver in 1996 (3.3 million compared to 1.8 million in Vancouver) (9,10). Population size and density are directly related to the number of automobiles and therefore levels of traffic-related air pollution in urban areas (11,12). While average NO₂ levels were comparable in Montreal and Vancouver in 2011 (~11-12 ppb), levels of particulate matter, another good indicator of traffic-related air pollution and air quality, were twice as high in Montreal than in Vancouver (13). Montreal is also generally considered to have worse air quality and greater air pollution than Vancouver and other Canadian cities such as Toronto when using air quality indicators such as ozone and particulate matter (14). The lack of variability in NO₂ levels in Vancouver may have limited the ability of this study to detect potential effects on risk of breast cancer if a non-linear relationship exists between NO₂ and breast cancer.

The LUR models for both Vancouver and Montreal are also fundamentally different in their creations, although both used similar covariates and modelling approaches. The Vancouver LUR model explained less variability in NO₂ compared to the Montreal LUR model (60% vs. 73%) (6,7). Another limitation may be the selection strategy of the controls: in the Vancouver-based case-control study for this project, the controls came from the mammography screening

program in Vancouver, while the controls in the Montreal case-control study were recruited from hospitals and were patients with cancers other than breast and bladder cancers (7). Importantly, only postmenopausal women were included in the Crouse study. Controls used in the Hystad national case-control study among women in eight provinces were population-based and women were recruited through a variety of methods such as random digit dialing and random sampling from health insurance plans (6). An important criticism of the Vancouver case-control design is the selection of controls from a screening program: women who attend screening programs are typically healthier, better educated, and wealthier than those who do not participate in screening programs, and this is apparent in the descriptive data reported here. These factors may also influence choice of residential neighborhood and in turn, exposure to traffic-related NO₂. This potential selection bias was addressed in a sensitivity analysis that restricted the analysis to those cases and controls who had participated in screening programs in the past, leading to a larger odds ratio comparable to that observed by Hystad et al. in women with premenopausal breast cancer. However, this analysis did not change the interpretation of the effect estimates for postmenopausal women, perhaps because most postmenopausal cases had previously participated in screening mammography programs (87% had previously participated in screening).

Despite adjusting for potential confounding by important risk factors for breast cancer including SES, education, and ethnicity, residual confounding may still exist, especially related to immigrant status, since those women not born in Canada are under-represented in the case group (48% of the cases were Canadian-born vs. 65% of the population in Vancouver in 1996, according to the national census) (9). Montreal has a larger population, almost twice as large compared to Vancouver in 1996 (3.3 million compared to 1.8 million in Vancouver) (9,10).

Population size and density is directly related to the number of automobiles and therefore levels of traffic-related air pollution in urban areas (11,12). In addition, Vancouver is home to nearly twice as many non-English and non-French speaking people than Montreal (33% compared to 18% of the population whose mother tongue was not French or English in 1996), twice as many immigrants (35% compared to 18% of the population in 1996), and almost three times the number of recent immigrants (11% compared to 4% of the population immigrated in the five years preceding the 1996 census) (9,10). The two study samples are likewise different. The majority of cases and controls (75%) in the Montreal study were white (French Canadian, Jewish or Italian) (7). In the Vancouver study, 57% of cases and 74% of controls were white, while 37% of cases and 22% of controls were Asian. Participants in the Montreal study were also better educated than participants in the Vancouver study. The majority of Montreal cases and controls had more than a community college degree while the majority of Vancouver cases and controls had the equivalent of or less than a community college degree.

Tobacco smoke is associated with exposure to numerous toxic chemicals including certain PAHs. It is therefore necessary to carefully control for tobacco use in any analysis evaluating the independent carcinogenic effects of traffic-related air pollution. Stratifying the analysis on smoking status can also provide additional insights about the absolute risk of traffic related air pollution (in the non-smoking population) and about potential interactions in the smoking population. In a case-control study conducted in Long Island (4), authors used a geographic traffic exposure dispersion model to estimate PAH exposure using BaP measurements and traffic counts. When the analyses were stratified on smoking status and menopausal status, significant associations between PAH exposure at time of menarche and breast cancer were only observed among non-smokers in the premenopausal model. A second

case-control study presented a pooled analysis using PAH-DNA adducts measured by ELISA in peripheral mononuclear cells (15). In this analysis of 873 cases and 941 controls, risk of breast cancer was increased for those with detectable PAH-DNA adducts when compared to non-detectable adduct levels (age-adjusted OR=1.29, 95% CI: 1.05, 1.58) (15). When stratified by cigarette smoking exposure, associations disappeared for former and current smokers (for non-smokers: OR=1.48, 95% CI: 1.10, 2.00; for former smokers: OR=1.23, 95% CI: 0.86, 1.76; for current smokers: OR=0.99, 95% CI: 0.62, 1.58). When the analyses were stratified by smoking status in this thesis project, no qualitative difference in effect estimates were observed (data not shown). However, these results are not directly comparable to the studies above, since PAH-DNA adducts were not measured in this project and NO₂ is not in itself hypothesized to be a cancer-causing agent, but rather a marker of a complex mixture of traffic-related air pollutants, which share some but not all the carcinogens in tobacco smoke.

In conclusion, most studies assessing the role of traffic-related air pollution and breast cancer have found inconsistent results pertaining to premenopausal and postmenopausal breast cancer and times of critical exposure. Evidence of a dose-response is limited and most studies suffer from limitations in exposure assessment. Broadly speaking, ecologic approaches highlight potential areas of future study, but more often on their own do not produce high-level evidence of biologic associations. Biomarker studies provide accurate information on biologically relevant exposure doses but may not necessarily reflect long-term exposure. Modelling approaches, such as land-use regression, have the ability to historically estimate exposures while controlling for geographic factors such as meteorology and topography. While these approaches do rely on routinely collected proxy indicators which are often not the carcinogenic agents of interest in

breast cancer etiology, the proxy indicators used are well correlated with the exposure of interest and NO₂ in particular is a widely used proxy measure of traffic-related air pollution.

5.3 Study validity: Methodological strengths and limitations

5.3.1 Selection bias

There are several strengths and limitations of this project that should be addressed when assessing the internal validity of this study. Case-control studies are always vulnerable to selection bias and this study is no exception. Newly diagnosed breast cancer cases were ascertained from the BC Cancer Registry and controls were recruited from the Screening Mammography Program (SMP) of British Columbia (BC), a population-based breast cancer-screening mammography program. Because of the variability in the access and use of the SMP in BC, there is a concern for a screening-related bias in this study (a type of volunteer bias). Women who attend screening mammography programs are typically more health-conscious (16), potentially better educated and wealthier.

Information on prior participation in a breast screening program was collected during the original interview with all participants. Consequently, it was possible to conduct sensitivity analysis excluding all cases who had never attended a breast cancer screening program, in an effort to ensure that the control group better reflected the underlying population that gave rise to the previously screened cases in the study. As described earlier, this sensitivity analysis led to a slightly higher OR for historical exposure to NO₂ and premenopausal breast cancer but not postmenopausal breast cancer.

It is also important to note that this case-control study essentially consists of volunteer patients and controls. If those cases and controls who agreed to participate differ systematically from the underlying eligible population of cases and controls, participation bias, a type of selection bias, may have been introduced. While the response rates do not differ much between the cases and the controls, they are, nevertheless, considered low (54% for cases and 57% for controls). All cases diagnosed in the study area during 2005 to 2010 were contacted. Controls from the same city-level area in British Columbia were frequency-matched to a five-year age group and were randomly selected from the SMP. Each eligible control was given a random number and was approached in the order of the random number. The study's principal investigators in Vancouver sent invitation letters to participate in the study to both cases and controls. The approach used to recruit cases and controls is unlikely to have caused any bias in the results with respect to NO₂ exposure. However, those that agreed to participate may be selectively different from those who did not participate with respect to important socio-demographic factors such as education and residential history. Unfortunately, the information required to compare responders to non-responders is not available. A comparison of the cases and controls suggests that more white women agreed to participate as controls, while a greater proportion of Asian women were recruited as cases. It is unlikely, however, that Asian women are in fact at higher risk for breast cancer in British Columbia and selection bias is likely an explanation for this observation. While it is difficult to control for selection bias, if information is available on the selection factors related to participation, controlling for these factors in the analysis can help minimize this bias. Therefore, most of the models described in this thesis are fully adjusted for socio-demographic factors and other breast cancer risk factors that may be related to participation in addition to NO₂ exposure.

Another related type of selection bias possible in the study population is the healthy immigrant effect, which occurs in high immigrant populations, such as that found in Vancouver. The healthy immigrant effect posits that people who have successfully immigrated are more likely to be healthy or health-conscious (17). In this study population, immigrants consumed significantly less alcohol and tobacco than Canadian-born participants. In the 1996 Canadian census, it was estimated that approximately 35% of Vancouver's population were immigrants (9). A sensitivity analysis excluding non-Canadian born participants was conducted to assess the healthy immigrant effect. This was a concern, in part, because a greater proportion of immigrants were cases and not controls. While the results of this analysis were not quantitatively different from the main analysis, the OR for historical exposure to NO₂ and postmenopausal breast cancer was larger than in any of the other analyses and was comparable to estimates of effect observed recently by Hystad et al. (OR=1.07 per 10 ppb increase in NO₂) (6). These results suggest that there may be a mild bias introduced into this study because of the high proportion of immigrants in Vancouver that were recruited as cases but not controls.

To further assess this bias, an additional analysis was conducted that excluded non-Canadian born participants and also excluded cases who had never attended screening mammography. Women who were born in Canada and had participated in prior screening were observed to have an OR_{5ppb} of 1.13 (95% CI: 0.85, 1.48) for the postmenopausal sample and an OR_{5ppb} of 1.37 (95% CI: 0.92, 2.05) for the premenopausal sample. The resulting odds ratios are the strongest produced from all the models although not statistically significant.

5.3.2 Information bias and measurement error

The strengths of this study include a relatively large study sample and a refined method of exposure assessment that provides a reasonable estimate of exposure at the individual-level. Compared to other exposure assessment methods, such as proximity to roads or biomarker measurements, land-use regression is able to combine not only pollutant measurements, but geographical features about the study area to improve prediction, and is able to estimate historical values for any year in the past, given measurements from fixed-site monitoring stations in that year. Exposure estimates also came from an independent data source and are unbiased.

Exposure to traffic-related air pollution was based on residential histories which were self-reported by participants in the questionnaire. Recall error (equal for cases and controls) is more of a concern especially for residential histories in the far past. The analyses for this project were limited to current residential address and residential address ten years prior to study entry. Participants were asked to give as much detail as possible and for as many addresses as they could remember, however many participants reported few addresses (on average 5.2 addresses) with limited data on years moved in and out. In the ten years before study entry, cases and controls provided on average 1.6 and 1.5 street addresses, respectively. A low proportion of women had more than three residences in the ten years prior to study entry (7.4% of cases and 5.6% of controls, see Table 4-1 for more information), suggesting recall bias is likely not a concern. There were errors in the residential history from the participants themselves, or from data entry which resulted in a number of addresses not being geocoded. For the second analysis, which required the address from ten years before study entry, the number of errors in these addresses also increased (see Section 4.2.1). However, these observable errors in recalling past

addresses did not differ between cases or controls. Therefore, this potential non-differential misclassification would have biased the effect estimate towards the null.

Measurement error may have arose due to the length of the questionnaire and concerns with data quality. While this questionnaire has not been formally validated, experts and peers in the field have used it previously. Studies have also shown that the length of questionnaires and surveys does not affect response quality, although variation in responses to questions nearer to the end of the questionnaire may be diminished (18,19). In general, the information used to derive covariates came from questions in the first half of the questionnaire.

The bigger concern in this study is measurement error associated with the exposure assessment for NO₂. The LUR model used was created by researchers at the University of British Columbia (1) and was able to explain 60% of the variability in the NO₂ data from the fixed-site monitors. In contrast, the LUR model used in the Crouse Montreal study explained 80% while the national LUR model in the Hystad study explained 73% of the variability in NO₂ concentrations (6,7). Additionally, when geocoding participants, the national Hystad study geocoded to the six-digit postal codes given in residential histories while the Montreal study and this study geocoded participants to their home residences. Postal codes are accurate proxies for residence locations in urban areas, but may confer misclassified estimates of exposure in rural areas (6). As stated in Section 3.5.1, the highest values in the LUR models were truncated to a more reasonable value, giving a higher proportion of people than otherwise expected the maximum exposure of NO₂ (30 ppb). This would have changed the distribution of NO₂, reducing the variability in cases and controls, which would have in turn decreased the ability of this study to find a true association, if there was one.

The method of back-extrapolation used involved inverse-distance weighting (IDW) fixed-site monitor measurements of historical NO₂ to create interpolation maps of Vancouver in the past. The IDW process creates a shape based on the furthest monitoring station point. Since what was available in 1995 to 2000 fell inside the limits of the LUR study area, the overall number of participants who lived within this smaller study area was fewer than those geocoded in the LUR model (see Figure 3-2). While it does not seem likely that either cases or controls systematically lived outside of the IDW area, there was a significant difference in the proportions of cases and controls who were excluded due to falling outside the IDW area ($p = 0.004$). Additionally, when 2003 LUR NO₂ concentrations for participants who fell within the IDW area and for those who fell outside were compared, a significant difference in NO₂ was found ($p < 0.001$). This was expected, as fixed-site monitors (used in the creation of the IDW surfaces) are utilized to monitor high-pollution areas. The overall distribution of NO₂ did not differ greatly when participants were excluded compared to the distribution of NO₂ of the full study population.

There are also inherent errors which occur within the geocoding process. However when a small random sample of the results of the software used was compared to another, coordinates given did not differ by more than 50 meters in >85% of the points. It is unlikely that any errors which did occur would systemically occur in one group over another; therefore the non-differential misclassification which possibly arose from this would bias the effect estimate towards the null. Two studies assessed the accuracy of positions geocoded compared to positions according to Global Positioning System (GPS) satellite receivers (20,21). For a random sample of addresses, the studies found 79-81% of addresses to be within 100 m of the GPS locations and concluded that address geocoding is very accurate.

NO₂ exposure assignment may have been highly misclassified due to a number of reasons. Assessment of NO₂ was based on home residence alone and for only two time points. Population mobility poses a major challenge to this exposure assessment approach since people do not necessarily spend all their time at home. A more accurate measure of exposure would have included the incorporation of NO₂ data from other locations where women spent much of their time, such as their workplace. Reassuringly, however, in 2002, Leech et al. found that Canadian adults spent 66% of time at home, indoors and outside combined (22). Another source of misclassification may have come from not using a larger sample of residential history to estimate exposure. In the analyses conducted, one address was used for each participant to estimate exposure to traffic-related air pollution. If a participant recently moved to the address from an area of higher or lower pollution, the exposure estimate assigned would not represent their true exposure. A sensitivity analysis was conducted including only participants who have lived at their address at study entry for the past ten years and effect estimates produced were slightly stronger than those in the original analyses, however not statistically significant. A better approach may be to estimate a time-weighted average of exposure over the entire residential history, similar to the analyses conducted by Hystad et al. (6). Misclassification produced from having many addresses does not appear to be systematically different between cases and controls and would therefore be non-differential. In addition, differences in individual behaviours may have also resulted in exposure misclassification. For example, the type of building a participant lived in may have affected their exposure estimate: the exposure associated with living on the top floor of a high-rise condominium may not be the same as the exposure assigned at ground-level of the same address. These are limitations due to the nature of the data collected although the

type of misclassification is most likely non-differential and would bias the estimate of effect towards the null.

Finally, assessing exposure to NO₂ further back in time may have been more appropriate for breast cancer due to its long latency. Hystad et al. modeled calculated 20-year averages, excluding women who had not provided at least 18 years of residential history (6). However, the data quality in this case-control study became increasingly compromised as women reported residential histories further than ten years back in time and there were fewer women with complete addresses in the Vancouver region as far back as 20 years (578 cases and 574 controls, approximately 60% of the original population, prior to stratification on menopausal status).

In summary, while residential histories were self-reported, participants were unlikely to systematically remember addresses better due to disease status, so recall bias is not thought to be an important concern, although possible non-differential misclassification from many sources remains an issue.

5.3.3 Confounding

In this study, a fully-adjusted model was presented to address some of the concerns with the screening-related bias and to allow for the comparison of results to two other Canadian studies that used an LUR approach to estimate the association between NO₂ and breast cancer, while adjusting for well-established and suspected risk factors for breast cancer. When compared to the age-adjusted models, in some cases, the effect estimates are quite different. Particularly in the results for the third and fourth sensitivity analyses, inclusion of all covariates in the final models greatly changed the effect estimates when exposure was estimated at ten years prior to

study entry (eg, the age-adjusted OR_{5ppb} for premenopausal women was 0.99 and the fully-adjusted OR_{5ppb} was 1.20 in the screening attendance sensitivity analysis, see Table 4.11B). This suggests possible bias or confounding may exist when the combination of covariates are not all included, although a confounder assessment exercise did not identify any individual confounders using the 10% minimum change-in-estimate approach (data not shown).

5.3.4 Study power and chance

In the proposal stage of this thesis project, power was calculated based on a number of assumptions about sample size and exposure distribution. Without extensively analyzing the study population prior to the proposal, it was assumed 876 cases and 824 controls were eligible for the study. In fact, the analysis with the smallest sample size was the fourth sensitivity analysis on premenopausal breast cancer (93 cases and 159 controls) – which results in a power of 72% when using the original assumptions about the exposure distribution. It was also assumed from the original LUR methods paper (1) that the exposure distribution of NO₂ was normally distributed (the paper reported that only the NO₂ measurements from the monitoring stations were normally distributed). When the actual distribution of estimated NO₂ from the LUR model was examined, cases and controls had a mean exposure of 18.1 ppb with a standard deviation of 3.8 ppb and was not normally distributed. Therefore, despite the high power calculated for this study, it is possible that power was overestimated given the assumption that the exposure was normally distributed. Furthermore, all of the analyses were stratified by menopausal status, which further reduced the study power. The calculation of post hoc power is also considered to have no additional insight once confidence intervals are constructed (23).

For all analyses, the confidence intervals (CI) for the odds ratios crossed the null value of one. It may be due to the lack of variation in the exposure: if a threshold effect exists for the relationship between NO₂ and breast cancer, this study may not have had the correct range of exposures to detect any real associations. Results were also somewhat inconsistent with the previous literature for the postmenopausal models, until certain exclusion criteria were applied. The sensitivity analyses may be the more robust analyses; however with reduced sample sizes, the ability to detect a statistically significant effect is diminished.

5.3.5 External validity

Assuming that the restricted and fully-adjusted effect estimates are the most reliable, these are the results that are potentially generalizable to the Vancouver population. However, as mentioned previously, these results may be modified by immigrant status and generalizability would then depend on the distribution of immigrants in the target population.

5.4 Conclusions and future research directions

The purpose of this thesis was to examine the association between traffic-related air pollution exposure and breast cancer incidence using estimated nitrogen dioxide (NO₂) as a proxy for traffic-related air pollution exposure. While the results for the two main analyses (the first using the home address at time of study entry to assign a NO₂ exposure for the year 2003 and the second using the home address ten years prior to study entry) were not statistically significant, effect estimates approached those observed in the previous literature in the sensitivity analyses conducted. Of note are the sensitivity analyses which excluded cases who have never

attended screening mammography and/or excluded participants who were not born in Canada. In these analyses, consistently increased odds ratios were observed for premenopausal women. Further research into the relationship between traffic-related air pollution and breast cancer is warranted, especially within the population of premenopausal women. Since there is a large immigrant population in the study region used in this thesis, future studies should focus on collecting large sample sizes in each immigrant status group to allow for more in-depth analyses.

Other future research should include nesting case-control studies within prospective cohort studies which routinely collect biologic samples. Currently, a large-scale prospective study is being conducted across Canada known as the Tomorrow Project (24). Biologic specimens are collected from participants and markers of air pollution exposure can be determined from these. Paolo Vineis at the London Imperial College in the UK is currently running a research program in Greece, Sweden, and Italy evaluating enviromarkers in the population to study the role of environmental agents (including traffic-related air pollution) in chronic disease causation (<http://www.enviromarkers.net/>). By using prospective cohort studies and nested case-control studies, factors that may influence ingestion and metabolism of pollutants can be identified (25).

Conducting a similar study in a city or cities with a larger range in NO₂ or traffic-related air pollutants would also improve power to detect smaller measures of effect. The method of exposure assessment used in this thesis, land-use regression, is limited as well in its assumption of how pollutants are distributed across an urban area. Increasingly, hybrid models are being used to assess air pollutant concentrations, combining methods such as land-use regression or interpolation with remote sensing (using satellite data) (26). These methods are cost-effective

and can be applied to large geographic areas; however the resolution of pollutant concentrations may not be sufficient enough to be applied at the level of an individual's house. Ideally, participants would be given personal air monitoring devices to measure personal exposures. Since this type of exposure assessment is only suited to prospective cohort studies, future studies using a similar method to LUR may use personal air monitoring devices to validate the estimates from the LUR models.

Finally, future research should include time activity diaries to capture information on time spent away from home and details about occupational and other exposures to air pollutants. This will allow for more accurate assessment of traffic-related air pollution exposure and help account for concerns of population mobility. If possible, assessing exposure at times thought to be critical to breast development, such as menarche or first pregnancy, may elucidate the nature and role of traffic-related air pollution in breast cancer etiology.

Given that ambient air pollution is a ubiquitous exposure that occurs in generally low concentrations in North America, using multiple and large cities will allow for the greatest ability to detect important associations, if they exist. The next step in environmental epidemiology research is to conduct nested case-control studies within large prospective studies, such as the Canadian Tomorrow Project, which routinely collects biologic specimens, to better ensure internally valid and robust methodological research.

5.5 References

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Appendix A

Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement 2, 2010" prepared by the Interagency Advisory Panel on Research Ethics for the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human participants be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. M. Evans, Community Member

Ms. J. Hudacin, Community Member

Mr. D. McNaughton, Community Member

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. M. Sawhney, Assistant Professor, School of Nursing, Queen's University

Dr. A. Singh, Professor, Department of Psychiatry, Queen's University

Dr. J. Walia, Assistant Professor and Clinical Geneticist, Department of Paediatrics, Queen's University and

Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

has reviewed the request for renewal of Research Ethics Board approval for the project "**Mapping the risk of postmenopausal breast cancer to exposure from traffic-related air pollution using land-use regression in Vancouver, BC**" as proposed by **Ms. N. Kwon** of the **Department of Public Health Sciences**, at **Queen's University**. The approval is renewed for one year, effective **June 26, 2014**. If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Albert F. Clark

Date: May 30, 2014

Chair, Health Sciences Research Ethics Board

Renewal 1[x] Renewal 2 [] Extension [] Code# EPID-432-13 Romeo file# 6010248

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards and operates in compliance with the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184, #IRB00001173

Current 2013 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital

Dr. M. Evans, Community Member

Dr. C. Godfrey, Assistant Professor, School of Nursing, Queen's University

Ms. J. Hudacin, Community Member

Dr. J. MacKenzie, Pediatric Geneticist, Department of Paediatrics, Queen's University

Mr. D. McNaughton, Community Member

Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. B. Simchison, Assistant Professor, Department of Anesthesiology and Perioperative Medicine, Queen's University

Dr. A. Singh, Professor, Department of Psychiatry, Queen's University

Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW

June 26, 2013

Ms. Nicollette Kwon
Department of Community Health and Epidemiology
Queen's Cancer Research Institute
Queen's University

Dear Ms. Kwon

Study Title: EPID-432-13 Mapping the risk of postmenopausal breast cancer to exposure from traffic-related air pollution using land-use regression in Vancouver, BC

File # 6010248

Co-Investigators: Dr. H. Richardson

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6010248 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file 6010248 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

A handwritten signature in cursive script that reads "Albert L. Clark".

Chair, Research Ethics Board
June 26, 2013

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

Appendix B

Canadian Breast Cancer Study Questionnaire

STUDY OF ENVIRONMENT, GENES AND BREAST HEALTH RESEARCH QUESTIONNAIRE

This questionnaire is part of a research study to understand the relationship between a woman's environment, her genes and breast health. The specific objectives are to investigate the association between exposure to certain environmental factors, including fossil fuels from vehicle exhaust, and light exposure at night, and breast diseases. We also wish to determine if some women are more genetically susceptible to exposures that would put them at higher risk for breast diseases.

Please prepare answers to the following questions to the best of your ability. If you choose to respond by telephone, we expect that it will take approximately one hour to collect your answers. If you are able to prepare your answers ahead of time, the interview should take less time. Alternatively, you may return this completed questionnaire by mail in the prepaid envelope provided.

The answers that you share with us will be strictly confidential and identified by an encrypted code, known by selected members of our research team only. Your honesty is important for the success of this research, and any answer is better than no answer.

We appreciate your cooperation tremendously.

Thank you!

GENERAL INFORMATION

Please answer each question as completely as possible. If you are unsure of an exact answer, give your best estimate.

Today's Date: _____
Month / day / year

1. When were you born? _____
Month / day / year

2. What is the highest grade of school you have completed?

- ☐ Some elementary (grade) school
- ☐ Completed elementary (grade) school
- ☐ Some secondary (high) school
- ☐ Completed secondary (high) school
- ☐ Trade certificate or diploma from a vocational school or apprenticeship training

- ☐ Certificate or diploma from a community college or CEGEP
- ☐ University degree (bachelor's degree)
- ☐ Graduate or professional school degree (above bachelor's degree)

3. What is your current employment status?

☐ employed (full-time)	☐ homemaker
☐ employed (part-time)	☐ student
☐ self-employed (full-time)	☐ retired
☐ self-employed (part-time)	☐ unemployed

4. Were you born in Canada? ☐ Yes
☐ No, I was born in

GENERAL INFORMATION (Cont'd)

5. How would you best describe you and your grandparent's race, ethnicity or colour?
Please specify as many as applicable:

Race, ethnicity or colour	Yourself	Your Maternal Grandmother	Your Maternal Grandfather	Your Paternal Grandmother	Your Paternal Grandfather
White	☐	☐	☐	☐	☐
Chinese	☐	☐	☐	☐	☐
South Asian (<i>e.g. East Indian, Pakistani, Punjabi, Sri Lankan</i>)	☐	☐	☐	☐	☐
Black	☐	☐	☐	☐	☐
Native/Aboriginal peoples of North America	☐	☐	☐	☐	☐
Arab/West Asian (<i>e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan</i>)	☐	☐	☐	☐	☐
Filipino	☐	☐	☐	☐	☐
South East Asian (<i>e.g. Cambodian, Indonesian, Laotian, Vietnamese</i>)	☐	☐	☐	☐	☐
Latin America	☐	☐	☐	☐	☐
Japanese	☐	☐	☐	☐	☐
Korean	☐	☐	☐	☐	☐
Other (<i>Specify</i>)					

HEALTH AND MEDICAL BACKGROUND

6. What is your height? _____ (feet and inches) **or** _____ (cm)
7. What is your current weight? ____ (lbs) **or** _____ (kg)
8. a) What was your weight 2 years ago? _____ (lbs) **or** _____ (kg)
b) What was your weight when you were 25 years old? _____ (lbs) **or** _____ (kg)
9. Not including pregnancy, what is the most you have weighed? ____ (lbs) **or** ____ (kg)
10. How old were you when you had your first menstrual period? ____ years of age
☐ Have never menstruated (*go to question #13*)
11. Are you still menstruating?
☐ Yes (*go to question #14*)
☐ No
↓
How many years has it been since your last menstrual period? ____ years
12. How did your menstrual periods stop?
☐ Naturally (through onset of menopause)
☐ As a result of a hysterectomy
☐ As a result of radiation or chemotherapy
☐ Other – please specify: _____
13. Have you ever had a hysterectomy (that is, an operation to remove the womb/uterus)?
☐ No
☐ Yes - at what age? ____ years
14. Have you ever had an oophorectomy (that is, an operation to remove one or both of your ovaries which is sometimes done at the same time as removal of the womb/uterus)?
☐ No
☐ Yes, one ovary removed: → at what age? _____ years
☐ Yes, second or both ovaries removed: → at what age? ____ years
☐ Don't know
15. Have you ever had a tubal ligation (that is, sterilization by having your “tubes tied”)?
☐ No
☐ Yes - at what age? ____ years

HEALTH AND MEDICAL BACKGROUND (Cont'd)

16. Have you ever taken fertility drugs (*e.g. Clomiphene, Clomid, Serophene, etc.*)

☐ No (*go to question #17*)

☐ Yes

Please provide details. If you don't remember the name, fill in the type, date started, date stopped and duration if possible. If you don't remember the month, please fill in the year. In calculating total duration, please include only the time periods that you used the specific medication.

Brand Name	Medication Type	Date Started (Month-Year)	Date Stopped (Month-Year)	Total Duration
<i>Example: Clomiphene</i>	<i>Pill</i>	<i>Sept-1999</i>	<i>Oct-2002</i>	<i>3 yrs</i>

17. Have you ever taken prescribed birth control medication for birth control or any other medical reason **for 6 months or more**? (*e.g. Norplant, Norinyl, Demulen, Depo-Provera, Tri-Cyclen, Alesse, etc.*)

☐ No (*go to question #18*)

☐ Yes

Please provide details. If you don't remember the name, fill in the type, date started, date stopped and duration if possible. If you don't remember the month, please fill in the year. In calculating total duration, please include only the time periods that you used the specific medication.

Brand Name	Medication Type	Date Started (Month-Year)	Date Stopped (Month-Year)	Total Duration
<i>Example: Norinyl</i>	<i>Pill</i>	<i>Sept-1990</i>	<i>Oct-1998</i>	<i>8 yrs</i>

HEALTH AND MEDICAL BACKGROUND (Cont'd)

18. Have you ever been prescribed antidepressants? (e.g. Fluoxetine (sold as Prozac), Nortriptyline (sold as Allegron), etc.)

☐ No (go to question #19)

☐ Yes

Please provide details. If you don't remember the name, fill in the type, strength, date started, date stopped and duration if possible. If you don't remember the month, please fill in the year. In calculating total duration, please include only the time periods that you used the specific medication.

Brand Name	Medication Type	Strength (milligrams)	Date Started (Month-Year)	Date Stopped (Month-Year)	Total Duration
<i>Example: Prozac</i>	<i>Pill</i>	<i>20</i>	<i>Nov-1990</i>	<i>Feb-1994</i>	<i>4 yrs</i>

19. Have you ever taken aspirin, ibuprofen or other nonsteroidal anti-inflammatory (NSAIDs) pain medication or tylenol or other acetaminophen pain medication for at least once per week for **6 months or longer**?

☐ No (go to question #20)

☐ Yes

Please provide details. If you don't remember the name, fill in the type, strength, number of tablets per week, date started, date stopped and duration if possible. If you don't remember the month, please fill in the year. In calculating total duration, please include only the time periods that you used the specific medication.

Brand Name	Medication Type	Strength (mg)	Number of Tablets/Week	Date Started	Date Stopped	Total Duration
<i>Example: Tylenol</i>	<i>Pill</i>	<i>200</i>	<i>28</i>	<i>Jan-1995</i>	<i>Nov-1995</i>	<i>11 months</i>

HEALTH AND MEDICAL BACKGROUND (Cont'd)

20. Have ever taken any type of female replacement hormones (presently known as hormone therapy or HT and previously called hormone replacement therapy or HRT? (e.g. *Estrace, Premarin, etc.*)

☐ Yes ☐ No (go to question# 22)

↓

Please provide details. If you don't remember the name, fill in the type, date started, date stopped and duration if possible. In calculating total duration, please include only the time periods that you used the specific medication.

Brand Name	Medication Type		Date		Total Duration
	Indicate if estrogen and/or progesterone	Indicate method of use (oral, patch, etc.)	Started (Month-Year)	Stopped (Month-Year)	
<i>Example: Premarin</i>	<i>Estrogen only</i>	<i>Oral</i>	<i>Feb-1963</i>	<i>Mar-1995</i>	<i>29 yrs</i>

21. Are you currently taking any type of hormone therapy or HT (e.g. *Estrace, Premarin, etc.*)?

☐ Yes ☐ No

The following questions are about screening for breast disease.

22. Have you ever had a mammogram (i.e. a breast x-ray)?

☐ Yes ☐ No (go to question #23)

↓

How old were you the first time you went for a mammogram? _____ years

What was the reason? _____

How many times have you had a mammogram since the first time? _____

When was the last time? (i.e. 6 months ago? 5 or more years ago?) _____

23. Have you ever examined your own breasts for lumps?

☐ Yes ☐ No (go to question #24)

↓

How old were you when you first started? _____ years

How often do you examine your breasts for lumps?

☐ Weekly ☐ Monthly ☐ Quarterly (every 3 months) ☐ Yearly
☐ Bi-weekly ☐ Bi-monthly ☐ Twice per year ☐ Unsure

HEALTH AND MEDICAL BACKGROUND (Cont'd)

24. These questions are about breast lumps or cysts that you had **more than a year ago**.

	Left breast	Right breast
Have you ever had a lump or cyst in your breast? <i>(if no to both left and right breast, go to question #25)</i>	Yes ☐ No ☐	Yes ☐ No ☐
How old were you when the first lump/cyst appeared?	Age _____ (years)	Age _____ (years)
Did you have any of the lumps/cysts examined by a doctor?	Yes ☐ No ☐	Yes ☐ No ☐
Did you have a biopsy or fine needle aspiration for any of the lumps/cysts?	Yes ☐ No ☐	Yes ☐ No ☐
Did a doctor diagnose any of the lumps/cysts as breast cancer?	Yes ☐ No ☐	Yes ☐ No ☐

PREGNANCY

25. Have you ever been pregnant? (include live births, still births, miscarriages and abortions)

☐ Yes ☐ No (go to question #26)

What is the total number of pregnancies? (include live births, still births, miscarriages and abortions) _____

Please fill in the following information for each of your pregnancies:

	Age at beginning of pregnancy (years)	Outcome	Weeks pregnancy lasted (weeks)	Number of months breast feeding
1 st Pregnancy		☐ Single live birth ☐ Multiple live births ☐ Stillbirth ☐ Miscarriage ☐ Abortion		☐ Not applicable ☐ Did not breast feed ☐ 1 - 2 months ☐ 3 - 4 months ☐ 5 - 6 months ☐ 7 - 12 months ☐ >12 months

	Age at beginning of pregnancy (years)	Outcome	Weeks pregnancy lasted (weeks)	Number of months breast feeding
2nd Pregnancy		☐ Single live birth ☐ Multiple live births ☐ Stillbirth ☐ Miscarriage ☐ Abortion		☐ Not applicable ☐ Did not breast feed ☐ 1 - 2 months ☐ 3 - 4 months ☐ 5 - 6 months ☐ 7 - 12 months ☐ >12 months

]

	Age at beginning of pregnancy (years)	Outcome	Weeks pregnancy lasted (weeks)	Number of months breast feeding
3rd Pregnancy		☐ Single live birth ☐ Multiple live births ☐ Stillbirth ☐ Miscarriage ☐ Abortion		☐ Not applicable ☐ Did not breast feed ☐ 1 - 2 months ☐ 3 - 4 months ☐ 5 - 6 months ☐ 7 - 12 months ☐ >12 months

Note: If more than 3 pregnancies, please use an additional page or the blank space on the following page. The interviewer will inquire about more, if applicable.

FAMILY

The next six questions will be asking about your family members and their history of cancer.

The first five questions (#26 - #30) are about your:

- parents
- full brothers
- full sisters
- children.

(A full sibling is one who has both the same mother and father as you.)

The sixth question (#31) concerns your other relatives and their history of cancer.

Please do not include relatives who joined your family by marriage or adoption.

Please answer the following questions to the best of your knowledge and complete the next 3 pages attached here for all relatives in each of the listed categories – regardless of whether they have or had cancer, they’re alive, or you haven’t seen or spoken to them for a while.

26. How many full brothers do you have? _____

27. How many full sisters do you have? _____

28. How many children do you have? _____

a. Number of sons? _____

b. Number of daughters? _____

FAMILY (Cont'd)

29. Please answer the following questions about your parents and siblings.

Relative	Year of birth	Have they ever been diagnosed with cancer?	Type(s) of cancer	Year of diagnosis	Are they alive?	If they're deceased, what year did they die?	If you're not sure they're alive, what year did you last hear from (or hear of) them?
Mother		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Father		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Full Sister 1		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Full Sister 2		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Full Brother 1		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Full Brother 2		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		

FAMILY (Cont'd)

30. This question is about your children. Please provide details on each of them.

Relative	Year of birth	Have they ever been diagnosed with cancer?	Type(s) of cancer	Year of diagnosis	Are they alive?	If they're deceased, what year did they die?	If you're not sure they're alive, what year did you last hear from (or hear of) them?
Son 1		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Son 2		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Daughter 1		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		
Daughter 2		☐ Yes ☐ No ☐ Don't know			☐ Yes ☐ No ☐ Don't know		

FAMILY (Cont'd)

31. This question is asking if **your father's parents, mother's parents, uncles, aunts, half-brothers, half-sisters, nephews or nieces** have ever had cancer. (A half-sibling is a brother or sister who has the same mother or father as you, but the other parent is different)

Are you aware of any such family members who have been diagnosed with cancer? Yes ☐ No ☐

If yes, please provide details on each of these relatives and whether they come from your mother's or father's side of your family.

Please do not include relatives who joined your family by marriage or adoption.

Relative	Mother's Side	Father's Side	Year of Birth	Year of Cancer Diagnosis	Type of Cancer	If deceased, year of death
	☐	☐				
	☐	☐				
	☐	☐				
	☐	☐				
	☐	☐				
	☐	☐				
	☐	☐				
	☐	☐				
	☐	☐				

LIFESTYLE HABITS (TOBACCO and ALCOHOL)

32. Have you ever smoked more than 100 cigarettes in your lifetime?
☐ Yes ☐ No (*go to question #37*)
33. How old were you when you STARTED smoking? _____ years of age
34. Are you currently smoking?
☐ Yes ☐ No - If no, at what age did you quit? _____ years
35. How many years in total have you smoked cigarettes? (excluding the years that you quit)
 _____ years
36. For the entire time you smoked, on average, how many cigarettes a day did you usually smoke?
 _____ cigarettes/day OR _____ cigarettes/week
37. This question asks about your family's smoking habits when you were 19 or younger.

FAMILY'S SMOKING HABITS	FATHER / GUARDIAN	MOTHER / GUARDIAN	OTHER MEMBER
Did your parent(s) or other household member(s) ever smoke in your presence when you were 19 or younger? (<i>go to question #38 if "no" for all</i>)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
For the entire time that s/he smoked, on average, how many cigarettes a day did s/he usually smoke? (cigarettes/day)	_____ cigarettes/day	_____ cigarettes/day	_____ cigarettes/day
What age were you when first exposed to your father's &/or mother's tobacco smoke? (years)	_____ years old	_____ years old	_____ years old
What age were you when no longer exposed to your father's &/or mother's tobacco smoke? (years)	_____ years old	_____ years old	_____ years old

38. During this time period (19 or younger), on average, how many hours per week were you exposed to someone else's tobacco smoke?

	Hours per week exposed to "second-hand" tobacco smoke						
	0	<1	1-2	3-4	5-6	7-9	>9
Age: 19 years and younger							

LIFESTYLE HABITS (TOBACCO and ALCOHOL) (Cont'd)

39. In the past (during different decades of your life), on average, **how many hours per week, outside of the workplace**, were you exposed to someone else's tobacco smoke?

	Hours per week exposed to "second-hand" tobacco smoke						
Age (decades)	0	<1	1-2	3-4	5-6	7-9	>9
20-29 years							
30-39 years							
40-49 years							
50-59 years							
2 years ago (if >60)							

40. This question asks about your alcohol consumption habits.

		Beer	Wine	Spirits
Have you ever drank the following more than twice a year? (if "no" to all 3, i.e. beer, wine and spirits, go to question #41)	Yes	☐	☐	☐
	No	☐	☐	☐
On average, how many drinks per week did you consume during different decades of your life? <i>One drink=1 glass of wine or 1 bottle of beer or 1 oz of spirits</i>				
Teens (15-19)?	Drinks/week OR < 1 time/month Never	___per wk ☐ ☐	___per wk ☐ ☐	___per wk ☐ ☐
20-29 years	Drinks/week OR < 1 time/month Never	___per wk ☐ ☐	___per wk ☐ ☐	___per wk ☐ ☐
30-39 years	Drinks/week OR < 1 time/month Never	___per wk ☐ ☐	___per wk ☐ ☐	___per wk ☐ ☐
40-49 years	Drinks/week OR < 1 time/month Never	___per wk ☐ ☐	___per wk ☐ ☐	___per wk ☐ ☐
50-59 years	Drinks/week OR < 1 time/month	___per wk	___per wk	___per wk

	Never	☐ ☐	☐ ☐	☐ ☐
2 years ago (if over 60 years of age)	Drinks/week OR < 1 time/month Never	____per wk ☐ ☐	____per wk ☐ ☐	____per wk ☐ ☐

LIFESTYLE HABITS (PHYSICAL ACTIVITY - HOUSEHOLD)

The next question (#41) refers to the frequency, duration and intensity of household activities.

The minimum number of hours for household activity to be included is:

- 2 hours per week, per year, or
- 7 hours per week for 4 months, if seasonal

Household activities (housework, yard work and home repair)

The three categories of physical intensity level for household activities are:

Light:

Activities that require minimal physical effort such as:

- **Home Activities** (sweeping, vacuuming, dusting, washing dishes, cooking, food preparation standing or sitting, putting away groceries, shopping, ironing, laundry)
- **Home Repair** (automobile repair, wiring, plumbing, carpentry, workshop)
- **Lawn and Garden** (watering lawn, fertilizing or seeding lawn, standing or walking in garden, mowing lawn on a rider mower)

Moderate:

Activities that are not exhausting, that increase the heart rate slightly and may cause some light perspiration such as:

- **Home Activities** (general house cleaning, food shopping with grocery cart, standing packing/unpacking boxes, occasional lifting of household items, child care – light effort)
- **Home Repair** (automobile body work, finishing or refinishing cabinets or furniture, caulking, laying tile or carpet, painting, papering, plastering, scraping, sanding floors, washing/waxing/painting a car or boat, washing fence).
- **Lawn and Garden** (mowing lawn by walking with a power mower, trimming shrubs or trees, operating a snow blower, planting seedlings, shrubs, trees, weeding, cultivating a garden, general gardening, sacking leaves, grass).

Heavy:

Activities that increase the heart rate and cause heavy sweating such as:

- **Home Activities** (major cleaning e.g. wash car, windows, mop, clean garage, sweeping sidewalk, scrubbing floors vigorous effort, moving household items, furniture, boxes), child care – moderate to heavy effort (e.g. walk/run-playing with children).
- **Home Repair** (outside carpentry, installing gutters, roofing, sawing hardwood, spreading dirt with a shovel, painting outside house).
- **Lawn and Garden** (carrying, stacking wood, lumber, chopping wood, splitting logs, clearing land, hauling branches, digging, spading, filling garden, laying sod, rock, mowing lawn with a push mower, shoveling snow by hand).

LIFESTYLE HABITS (PHYSICAL ACTIVITY - HOUSEHOLD)

41. Please report household activities (housework, yard work and home repair) that you have done over your lifetime. It may help you to consider what a typical day is for you. Then think about how many hours of household and gardening or yard work you do in a typical day. Sedentary activities like sewing or bookkeeping are not included. *You may list activities individually or group them as in the examples listed on page 15.*

No.	Description of Household Activity	Age Started	Age Ended	Frequency of Activity					Time per activity		Intensity of Household Activity* (Please check one for each activity)
				Days /week	Weeks /month	Months /year	Years	Hours	Minutes		
eg. 1	Home Activities	12	18	3	4	12	6	1		☒ Light ☐ Moderate ☐ Heavy	
eg. 2	Childcare	24	32	7	4	12	8	10		☐ Light ☒ Moderate ☐ Heavy	
1										☐ Light ☐ Moderate ☐ Heavy	
2										☐ Light ☐ Moderate ☐ Heavy	
3										☐ Light ☐ Moderate ☐ Heavy	
4										☐ Light ☐ Moderate ☐ Heavy	
5										☐ Light ☐ Moderate ☐ Heavy	
6										☐ Light ☐ Moderate ☐ Heavy	
7										☐ Light ☐ Moderate ☐ Heavy	
8										☐ Light ☐ Moderate ☐ Heavy	
9										☐ Light ☐ Moderate ☐ Heavy	

* For definition of Intensity of household activity, please see list on previous page.

Intensity of household activities defined as:

Light = activities that require minimal effort,

Moderate = activities that are not exhausting, that increase the heart rate slightly and that may cause some light perspiration,

Heavy = activities that increase the heart rate and cause heavy sweating.

LIFESTYLE HABITS (PHYSICAL ACTIVITY – SPORTS AND EXERCISE)

The next question (#42) refers to the frequency, duration and intensity of exercise and sports activities.

The minimum number of hours for an exercise and sports activity to be included is:

- **32 hours total per year, or**
- **40 minutes per week, per year, or**
- **2 hours per week for 4 months, if seasonal**

The three categories of physical intensity level for exercise and sports activities are:

Light: Activities that require minimal physical effort such as those activities that are done standing or with slow walking

Moderate: Activities that are not exhausting, that increase the heart rate slightly and may cause some light perspiration

Heavy: Activities that increase the heart rate and cause heavy sweating.

If you have multiple episodes of the same activity over the years, record each episode separately. If there is a change in the frequency (months or days) or duration (hours) of the activity without actually discontinuing the activity for a certain length of time, a new line should be started because of the change in pattern.

An example of how to work with the table:

Activities:

from 8 yrs to 16 yrs played soccer- 1.5 hours per day, 2 days per week, 4 weeks per month, 4 months per year

from 25 yrs to 29 yrs played soccer - 2 hours per day, 2 days per week, 4 weeks per month, 8 months per year

from 18 to 49 played golf - 3 hours per day, 1 day per week, 4 weeks per month, 4 months per year

No.	Description of Exercise / Sports Activity	Age Start	Age End	Frequency of Activity				Time per activity		Intensity of Leisure Activity* (Please check one for each activity)
				Days /week	Weeks /month	Months /year	Years	Hours	Minutes	
1	Soccer	8	16	2	4	4	8	1	30	☐ Light ☐ Moderate ☒ Heavy
2	Soccer	25	29	2	4	8	4	2		☐ Light ☐ Moderate ☒ Heavy
3	Golf	18	49	1	4	4	31	3		☒ Light ☐ Moderate ☐ Heavy

LIFESTYLE HABITS (PHYSICAL ACTIVITY – SPORTS AND EXERCISE) (Cont'd)

42. This question asks about exercise or sports activities that you did during your lifetime starting with childhood. Please report the activities that you have done at **least 2 hours per week for at least 4 months** of the year. Please begin by entering the activities that you did during your school years.

No.	Description of Exercise/Sports Activity	Age Started	Age Ended	Frequency of Activity					Time per activity		Intensity of Leisure Activity* (Please check one for each activity)
				Days /week	Weeks /month	Months /year	Years	Hours	Minutes		
eg.	Soccer	9	18	3	4	4	9	1			☐ Light ☐ Moderate ☒ Heavy
1											☐ Light ☐ Moderate ☐ Heavy
2											☐ Light ☐ Moderate ☐ Heavy
3											☐ Light ☐ Moderate ☐ Heavy
4											☐ Light ☐ Moderate ☐ Heavy
5											☐ Light ☐ Moderate ☐ Heavy
6											☐ Light ☐ Moderate ☐ Heavy
7											☐ Light ☐ Moderate ☐ Heavy
8											☐ Light ☐ Moderate ☐ Heavy
9											☐ Light ☐ Moderate ☐ Heavy

* Intensity of exercise/sports activity defined as:

Light = activities that require minimal effort,

Moderate = activities that are not exhausting, that increase the heart rate slightly and that may cause some light perspiration,

Heavy = activities that increase the heart rate and cause heavy sweating.

LIFESTYLE HABITS (SMOKED/GRILLED FOODS)

43. During different decades of your life, how often did you usually eat meat or fish that had been smoked or that had a strong smoky taste?

Age (decades)	Times/week OR	Times/month OR	Times/year OR	Never/Almost never
Teen's (12-19)				☐
20-29 years				☐
30-39 years				☐
40-49 years				☐
50-59 years				☐
2 years ago				☐

44. During different decades of your life, how often did you usually eat pickles or other pickled foods?

Age (decades)	Times/week OR	Times/month OR	Times/year OR	Never/Almost never
Teen's (12-19)				☐
20-29 years				☐
30-39 years				☐
40-49 years				☐
50-59 years				☐
2 years ago				☐

45. During different decades of your life, how often did you usually eat charcoal-grilled foods in the summer?

Age (decades)	Times/week OR	Times/month OR	Times/year OR	Never/Almost never
Teen's (12-19)				☐
20-29 years				☐
30-39 years				☐
40-49 years				☐
50-59 years				☐
2 years ago				☐

46. During different decades of your life, how often did you usually eat charcoal-grilled foods in the **winter**?

Age (decades)	Times/week OR	Times/month OR	Times/year OR	Never/Almost never
Teen's (12-19)				☐
20-29 years				☐
30-39 years				☐
40-49 years				☐
50-59 years				☐
2 years ago				☐

Congratulations!!

You are over halfway there!!

The next portion of the questionnaire relates to residential and occupational history. Please take a moment to stretch your legs and pour a cup of tea if you wish before beginning this section.

... and please also remember that by completing this questionnaire you are contributing to very important research and your generous gift of time is very much appreciated!

RESIDENTIAL HISTORY (GENERAL)

47. Please list the addresses in which you have lived for 1 year or more, throughout your lifetime, ending with your current address. We understand that it may be difficult to recall detailed information for all residences throughout your lifetime and would appreciate it if you would enter as much information as you are able.

	What was the address of the (first/next) place you lived in for 1 year or more? (If residence is outside of Canada, city and country will be fine)	What year did you start living there?	What year did you move from there?	How many years did (have) you lived there?	Type of Residence?
1st	Street, apt # _____ City/Town _____ (or Country if outside Canada) _____ Postal code _____ Province _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
2nd	Street, apt # _____ City/Town _____ (or Country if outside Canada) _____ Postal code _____ Province _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
3rd	Street, apt # _____ City/Town _____ (or Country if outside Canada) _____ Postal code _____ Province _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
4th	Street, apt # _____ City/Town _____ (or Country if outside Canada) _____ Postal code _____ Province _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
5th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other

RESIDENTIAL HISTORY (GENERAL) (Cont'd)

47. (Cont'd)

	What was the address of the (first/next) place you lived in for 1 year or more? (If residence is outside of Canada, city and country will be fine)	What year did you start living there?	What year did you move from there?	How many years did (have) you lived there?	Type of Residence?
6th	<u>Street, apt #</u> <u>City/Town</u> <u>Province (or Country if outside Canada)</u> <u>Postal code</u>	<u>Date</u>	<u>Date</u>	<u>Years</u>	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
7th	<u>Street, apt #</u> <u>City/Town</u> <u>Province (or Country if outside Canada)</u> <u>Postal code</u>	<u>Date</u>	<u>Date</u>	<u>Years</u>	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
8th	<u>Street, apt #</u> <u>City/Town</u> <u>Province (or Country if outside Canada)</u> <u>Postal code</u>	<u>Date</u>	<u>Date</u>	<u>Years</u>	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
9th	<u>Street, apt #</u> <u>City/Town</u> <u>Province (or Country if outside Canada)</u> <u>Postal code</u>	<u>Date</u>	<u>Date</u>	<u>Years</u>	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
10th	<u>Street, apt #</u> <u>City/Town</u> <u>Province (or Country if outside Canada)</u> <u>Postal code</u>	<u>Date</u>	<u>Date</u>	<u>Years</u>	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other

RESIDENTIAL HISTORY (GENERAL) (Cont'd)

If more than 10 residences apply, please continue:
47. (Cont'd)

	What was the address of the (first/next) place you lived in for 1 year or more? (If residence is outside of Canada, city and country will be fine)	What year did you start living there?	What year did you move from there?	How many years did (have) you lived there?	Type of Residence?
11th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
12th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
13th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
14th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
15th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	Date _____	Date _____	Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other

47. (Cont'd)

	What was the address of the (first/next) place you lived in for 1 year or more? (If residence is outside of Canada, city and country will be fine)	What year did you start living there?	What year did you move from there?	How many years did (have) you lived there?	Type of Residence?
16th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	_____ Date _____	_____ Date _____	_____ Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
17th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	_____ Date _____	_____ Date _____	_____ Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
18th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	_____ Date _____	_____ Date _____	_____ Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
19th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	_____ Date _____	_____ Date _____	_____ Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other
20th	Street, apt # _____ City/Town _____ Province (or Country if outside Canada) _____ Postal code _____	_____ Date _____	_____ Date _____	_____ Years _____	☐ City ☐ Suburb ☐ Town ☐ Rural ☐ Other

Note: If more than 20 residences, please use an additional page or the back of this questionnaire. Interviewer will inquire about more residences, if applicable.

RESIDENTIAL HISTORY (SOURCES OF ENERGY)

48. Now I would like to know about the sources of energy available at each of these residences (place a check mark in those boxes that apply).

		1 st Res	2 nd Res	3 rd Res	4 th Res	5 th Res	6 th Res	7 th Res	8 th Res	9 th Res	10 th Res
A What is (was) the <u>major</u> source of energy for the oven or appliance used for cooking at this address?	Electricity?										
	Natural gas?										
	Wood fire?										
	Other? <i>(Please specify)</i>										
	Not sure?										
B What is (was) the <u>major</u> source of energy for the furnace or the major source of heat at this address?	Electricity?										
	Natural gas?										
	Oil?										
	Fireplace?										
	Wood/Gas Stove?										
	Other? <i>(Please specify)</i>										
	Not sure?										
	Wood?										
	Coal?										
	Gas?										
C If answer to B was fireplace or wood/gas stove, what materials did you usually burn?	Other? <i>(Please specify)</i>										
	Not sure?										
	Wood?										
	Coal?										
	Gas?										
D If you used(d) a fireplace or wood/gas stove for additional heat or other purpose at this address, what materials did you usually burn? (Check all that apply)	Other? <i>(Please specify)</i>										
	Not sure?										
	Wood?										
	Coal?										
	Gas?										
	Synthetic logs?										
	Other? <i>(Please specify)</i>										
	Not sure?										

RESIDENTIAL HISTORY (SOURCES OF ENERGY)

If more than 10 residences apply, please continue:
48. (Cont'd)

		11 th Res	12 th Res	13 th Res	14 th Res	15 th Res	16 th Res	17 th Res	18 th Res	19 th Res	20 th Res
A	What is (was) the major source of energy for the oven or appliance used for cooking at this address?	Electricity?									
		Natural gas?									
		Wood fire?									
		Other? (Please specify)									
		Not sure?									
B	What is (was) the major source of energy for the furnace or the major source of heat at this address?	Electricity?									
		Natural gas?									
		Oil?									
		Fireplace?									
		Wood/Gas Stove?									
		Other? (Please specify)									
		Not sure?									
C	If answer to B was fireplace or wood/gas stove, what materials did you usually burn?	Wood?									
		Coal?									
		Gas?									
		Other? (Please specify)									
		Not sure?									
D	If you use(d) a fireplace or wood/gas stove for additional heat or other purpose at this address, what materials did you usually burn? (Check all that apply)	Wood?									
		Coal?									
		Gas?									
		Synthetic logs?									
		Other? (Please specify)									
		Not sure?									

Note: If more than 20 residences, please note this information on the additional page. Interviewer will inquire about more residences, if applicable.

RESIDENTIAL HISTORY (GENERAL ENVIRONMENT)

49. Now I would like to know a little about the indoor and outdoor environment of each of these residences. Place a check mark in those boxes that apply.

☐ Please check here if these options do not apply to any of your residences

OUTDOOR ENVIRONMENT										
Were any of these residences situated within one kilometer (~6 blocks) of:										
	1st Res	2nd Res	3rd Res	4th Res	5th Res	6th Res	7th Res	8th Res	9th Res	10th Res
An airport?										
A railroad?										
An industrial site?										
A multi-lane highway (two lanes or more)?										
If more than 10 residences, please continue:										
	11th Res	12th Res	13th Res	14th Res	15th Res	16th Res	17th Res	18th Res	19th Res	20th Res
An airport?										
A railroad?										
An industrial site?										
A multi-lane highway (two lanes or more)?										

Note: If more than 20 residences, please note this information on the additional page. Interviewer will inquire about more residences, if applicable.

RESIDENTIAL HISTORY (INDOOR ENVIRONMENT)

50. Which best describes the ambient light in your bedroom, when you were sleeping at each of these residences?

Dark=could not see hand in front of face or wore a mask in bed Medium=could see to the end of the bed Light=could almost read without a light										
	1st Res	2nd Res	3rd Res	4th Res	5th Res	6th Res	7th Res	8th Res	9th Res	10th Res
Ambient light in bedroom at each residence	Dark ☐ Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐
If more than 10 residences, please continue:										
Ambient light in bedroom at each residence	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐	Dark ☐ Med ☐ Light ☐

Note: If more than 20 residences, please note this information on the additional page. Interviewer will inquire about more residences, if applicable.

51. Now I would like to know about your usual sleeping habits throughout different decades of your life.

	12 - 19	20- 29	30 - 39	40 - 49	50 - 59	In the last 2 years
Average time the lights were turned off for bed						
Average time when you woke-up						
If sleep was interrupted, were lights usually turned on?	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Were lights usually turned on for more than 1 hour?	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO

EMPLOYMENT HISTORY

52. Please tell us about EACH job or occupation you had for **at least** 6 months, including volunteer and military service, but not including schooling or homemaking. Include only seasonal or part-time work that is equivalent to 6 months or more. Begin with your most recent job and continue back to your first job. Include any absences from the work force and jobs you have done outside of Canada.

Job No.	Time Period		Type of Industry, Business or Service	Company Name and Location	Job Title	Rate of Intensity* (Please check one for each job)
	Start (Month-Year)	End (Month-Year)				
Eg.	Nov-1993	Feb-2003	Hairdressing	Suki's Hair Salon, Vancouver, BC	Colour Specialist	☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
1						☐ Sedentary ☐ ☐ Moderate ☐ Light ☐ Heavy
2						☐ Sedentary ☐ ☐ Moderate ☐ Light ☐ Heavy
3						☐ Sedentary ☐ ☐ Moderate ☐ Light ☐ Heavy
4						☐ Sedentary ☐ ☐ Moderate ☐ Light ☐ Heavy
5						☐ Sedentary ☐ ☐ Moderate ☐ Light ☐ Heavy

* Intensity of job or occupation defined as:

Sedentary = work that involves sitting only, with minimal walking,

Light = work that involves minimal physical effort such as standing and slow walking with no increase in heart rate and no perspiration,

Moderate = work that is not exhausting, that increases the heart rate slightly and may cause some light perspiration, such as those that require carrying light loads (5-10 lbs) or that have continuous walking,

Heavy = work that is vigorous, increases the heart rate substantially and causes heavy sweating such as those that involve lifting, carrying heavy loads (>10 lbs), brisk walking, or climbing.

Note: Space for more jobs is on the next page.

EMPLOYMENT HISTORY (Cont'd)

52. (Cont'd) *Note: If more than 12 jobs, please use an additional page. Interviewer will inquire about more jobs, if applicable.*

Job No.	Time Period		Type of Industry, Business or Service	Company Name and Location	Job Title	Rate of Intensity* (Please check one for each job)
	Start (Month- Year)	End (Month- Year)				
6						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
7						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
8						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
9						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
10						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
11						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy
12						☐ Sedentary ☐ Moderate ☐ Light ☐ Heavy

* Intensity of job or occupation defined as:

Sedentary = work that involves sitting only, with minimal walking.

Light = work that involves minimal physical effort such as standing and slow walking with no increase in heart rate and no perspiration.

Moderate = work that is not exhausting, that increases the heart rate slightly and may cause some light perspiration, such as those that require carrying light loads (5-10 lbs) or that have continuous walking.

Heavy = work that is vigorous, increases the heart rate substantially and causes heavy sweating such as those that involve lifting, carrying heavy loads (>10 lbs), brisk walking, or climbing.

EMPLOYMENT HISTORY (Cont'd)

53. Please tell us about the corresponding work shift for each job you listed

Job No.	Average number of hours worked per week	Percentage of time worked at each shift			Usual hours worked at each shift					
		Day shifts	Evening shifts	Late-night shifts (work through midnight)	Day shifts		Evening shifts		Late-night shifts	
					Start	End	Start	End	Start	End
eg.	35	80%	20%		10:00 am	5:30 pm	5:30 pm	9:00 pm		
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										

Note: If more than 12 jobs, please use an additional page. Interviewer will inquire about more jobs, if applicable.

EMPLOYMENT HISTORY (Cont'd)

54. Please tell us about the corresponding exposures to passive smoking and engine exhausts for each job you listed. In addition, could you tell us the mode of transport used to commute to each job listed

Job No.	At this job, on average, about how many people around you smoked?	While on this job, did you ever work near diesel engines or other types of engines?	While on this job, did you ever smell diesel exhaust or other types of engine exhaust?	How did you usually commute to this job?
1	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
2	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
3	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
4	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
5	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
6	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure

Note: Space for more jobs is on the next page.

EMPLOYMENT HISTORY (Cont'd)

54 (Cont'd)

Job No.	At this job, on average, about how many people around you smoked?	While on this job, did you ever work near diesel engines or other types of engines?	While on this job, did you ever smell diesel exhaust or other types of engine exhaust?	How did you usually commute to this job?
7	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
8	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
9	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
10	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
11	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure
12	☐ 0 smokers ☐ <10 ☐ 11 –19 ☐ 20 or more ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Yes ☐ No ☐ Not sure	☐ Bus/Tramway ☐ Metro/Train ☐ Car ☐ Bicycle ☐ No Commute ☐ Motorcycle ☐ Foot ☐ Other ☐ Truck ☐ Not sure

Note: If more than 12 jobs, please use an additional page. Interviewer will inquire about more jobs, if applicable.

EMPLOYMENT HISTORY (Cont'd)

55. Referring to the jobs you listed in question #52, we would like to know if you ever worked for **more than 6 months** in any of the following specific jobs. If your work in any of these industries involved *primarily* office and administrative tasks, please indicate this by checking the box in the far right column.

Industry		Job number(s) from Question 52	Office/Admin.
Aircraft maintenance	Yes ☐ No ☐		☐
Building construction	Yes ☐ No ☐		☐
Fire-fighting	Yes ☐ No ☐		☐
Maritime industry	Yes ☐ No ☐		☐
Food services	Yes ☐ No ☐		☐
Landscaping	Yes ☐ No ☐		☐
Agriculture	Yes ☐ No ☐		☐
Gas distribution as station attendant	Yes ☐ No ☐		☐
Postal services as mail carrier	Yes ☐ No ☐		☐
Mining	Yes ☐ No ☐		☐
Oil refining industry	Yes ☐ No ☐		☐
Police detachment	Yes ☐ No ☐		☐
Plumbing	Yes ☐ No ☐		☐
Road construction and maintenance	Yes ☐ No ☐		☐
Roofing	Yes ☐ No ☐		☐
Waterproofing	Yes ☐ No ☐		☐
Rubber industry	Yes ☐ No ☐		☐
Metalworking	Yes ☐ No ☐		☐
Traffic/warehousing/shipping	Yes ☐ No ☐		☐
Production of coke	Yes ☐ No ☐		☐
Manufacture of electrodes	Yes ☐ No ☐		☐
Gas works	Yes ☐ No ☐		☐
Tar distillery	Yes ☐ No ☐		☐
Production of aluminum	Yes ☐ No ☐		☐

EMPLOYMENT HISTORY (Cont'd)

56. In any of your jobs we have already asked about, did you carry out any of the following tasks?

Tasks		Job number(s) from Question 52
Operating a boat engine	Yes ☐ No ☐	
Metal working (grinding, cutting, extruding, machining)	Yes ☐ No ☐	
Furnace work	Yes ☐ No ☐	
Fire fighting	Yes ☐ No ☐	
Cooking	Yes ☐ No ☐	
Baking bread products or pastries	Yes ☐ No ☐	
Operating coke oven	Yes ☐ No ☐	
Chimney sweeping	Yes ☐ No ☐	
Brick-laying	Yes ☐ No ☐	
Masonry	Yes ☐ No ☐	
Carpentry	Yes ☐ No ☐	
Repair electrical equipment or fixtures	Yes ☐ No ☐	
Driving a forklift	Yes ☐ No ☐	
Bartending	Yes ☐ No ☐	
Waitressing	Yes ☐ No ☐	
Gardening	Yes ☐ No ☐	
Waste incineration	Yes ☐ No ☐	

57. In any of your jobs we have already asked about, did you handle any of the following materials?

Materials		Job number(s) from Question 52
Coal tar	Yes ☐ No ☐ Don't Know ☐	
Pitch	Yes ☐ No ☐ Don't Know ☐	
Asphalt	Yes ☐ No ☐ Don't Know ☐	
Bitumen	Yes ☐ No ☐ Don't Know ☐	
Creosote	Yes ☐ No ☐ Don't Know ☐	
Soot	Yes ☐ No ☐ Don't Know ☐	
Anthracene oil	Yes ☐ No ☐ Don't Know ☐	
Cutting oils	Yes ☐ No ☐ Don't Know ☐	

INCOME

The following 2 questions are related to your household income. This information is very important and will only be used for the purposes of this research study. Please be assured that, like all other information you have provided, these answers will be kept strictly confidential.

58. **Thinking back to 2 years ago**, how many people were living in your household at that time? _____

59. **Thinking back to 2 years ago**, what was the **total income** for all people living in your household **from all sources, before taxes**? Sources include income from all earnings (wages and salaries), income from all government sources and all investment income (such as retirement funds).

☐ No income	☐ \$40,000 to \$59,999
☐ Less than \$15,000	☐ \$60,000 to \$79,999
☐ \$15,000 to \$19,999	☐ \$80,000 to \$99,999
☐ \$20,000 to \$29,999	☐ \$100,000 or more
☐ \$30,000 to \$39,999	☐ Not Stated

Thank you very much for completing this questionnaire!
Because we want to be able to use all the information you have provided, we would greatly appreciate it if you would please take a moment to review each page making sure that you did not skip any pages.

In the space below, please add any comments you wish, and thank you again for the information you have provided!

Appendix C

Additional Data Tables

Table C-1: Bivariate analyses for post- and premenopausal women for all covariates, except age (matching variable)

CHARACTERISTICS	POSTMENOPAUSAL WOMEN (N=1,196)	PREMENOPAUSAL WOMEN (N=711)
	OR (95% CI)	OR (95% CI)
ETHNICITY		
White	1	1
East Asian	2.88 (2.08, 3.99)	2.43 (1.70, 3.48)
Other	1.86 (1.31, 2.66)	1.35 (0.88, 2.09)
EDUCATION, highest level achieved		
High school or less	1	1
Trade certificate/Completed community college/CEGEP	0.67 (0.50, 0.90)	0.74 (0.48, 1.15)
University, graduate, or professional degree	0.50 (0.38, 0.66)	0.56 (0.38, 0.85)
HOUSEHOLD INCOME		
< \$40,000	1	1
\$40,000 to \$59,999	0.57 (0.39, 0.84)	0.60 (0.35, 1.03)
\$60,000 to \$79,999	0.47 (0.30, 0.74)	0.43 (0.24, 0.79)
\$80,000 to ≥ \$100,000	0.52 (0.32, 0.86)	0.50 (0.27, 0.92)
No income	0.60 (0.39, 0.91)	0.25 (0.13, 0.49)
Not stated	0.31 (0.21, 0.47)	0.48 (0.29, 0.78)

	POSTMENOPAUSAL WOMEN (N=1,196)	PREMENOPAUSAL WOMEN (N=711)
CHARACTERISTICS	OR (95% CI)	OR (95% CI)
# FIRST-DEGREE RELATIVES WITH BREAST CANCER		
None	1	1
At least one	1.65 (1.22, 2.24)	1.45 (0.95, 2.22)
AGE AT MENARCHE	1.06 (0.99, 1.14)	0.96 (0.87, 1.07)
AGE AT FIRST BIRTH		
Never pregnant	1	1
< 29	1.27 (0.92, 1.76)	1.47 (0.96, 2.27)
≥ 29	1.13 (0.81, 1.58)	1.62 (1.12, 2.35)
# OF PREGNANCIES		
0	1	1
< 2	1.57 (1.02, 2.42)	1.81 (1.12, 2.92)
≥ 2	1.14 (0.84, 1.55)	1.53 (1.07, 2.2)
DURATION OF BREASTFEEDING, months		
< 12	1	1
12 to < 24	0.67 (0.48, 0.93)	0.70 (0.48, 1.02)
≥ 24	0.87 (0.59, 1.29)	0.82 (0.50, 1.37)
AGE AT BILATERAL OOPHORECTOMY		
Never had	1	N/A
< 40	0.93 (0.38, 2.24)	N/A
40 to < 50	0.93 (0.53, 1.64)	N/A

	POSTMENOPAUSAL WOMEN (N=1,196)	PREMENOPAUSAL WOMEN (N=711)
CHARACTERISTICS	OR (95% CI)	OR (95% CI)
≥ 50	0.87 (0.51, 1.49)	N/A
OC USE		
Never used	1	1
Used	0.71 (0.56, 0.90)	0.42 (0.31, 0.58)
HRT USE		
Never used	1	1
Used	0.92 (0.73, 1.16)	0.76 (0.39, 1.47)
AVERAGE ALCOHOL CONSUMPTION, drinks/week based on age	0.87 (0.84, 0.91)	0.88 (0.83, 0.93)
SMOKING STATUS		
Non-smoker	1	1
Former	0.91 (0.72, 1.16)	0.89 (0.64, 1.24)
Current	0.92 (0.58, 1.46)	0.72 (0.38, 1.40)
AVERAGE LIFETIME PACKYEARS	1.00 (1.00, 1.01)	1.01 (0.99, 1.03)
BMI, kg/m²	1.05 (1.02, 1.07)	0.98 (0.96, 1.02)