BUILT ENVIRONMENT AND POST-MENOPAUSAL BREAST CANCER RISK: ANALYSIS OF A LINKED BRITISH COLUMBIAN COHORT

by

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B.Sc., The University of Victoria, 2017

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

April 2021

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Built Environment and Post-menopausal Breast Cancer: Analysis of a Linked British Columbian Cohort

submitted by Sean Harrigan in partial fulfillment of the requirements for

the degree of: Master of Science

in Population and Public Health

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Abstract

Background: Breast cancer is the most common type of cancer worldwide and the second leading cause of cancer deaths in women.[1–5] Up to 50% of breast cancer cases are preventable, underscoring the importance of research into underlying risk factors, especially for post-menopausal women.[6] With urbanization rates increasing in recent decades, the built environment may contain an important yet understudied set of modifiable breast cancer risk factors.[7]

Objectives: To evaluate the impact of three factors of the built environment– traffic-related air pollution (TRAP), measured using NO_2, walkability, and residential greenness – on risk of breast cancer in post-menopausal women in the Lower Mainland of British Columbia (BC).

Methods: This research was conducted using BC Generations Project[8] cohort and linked CANUE[9] environmental datasets. Descriptive statistics summarized socio-demographic, behavioural and health indicators in relation to the built environment. Cox proportional hazard regression was used to model cancer risk for three built environmental factors, while adjusting for relevant confounders. A change-in-effect model building strategy was used.

Results: The study included 7,330 participants, including 122 incident breast cancer cases. The HR for a 10-ppb increase in baseline NO_2 was 1.45 (95% CI=0.90, 2.33; p=0.12), whereas the HR for NO_2 averaged over the years 1980-2012 was 1.41 (95% CI=0.95, 2.08; p = 0.09), both adjusting for body mass index and social deprivation. The walkability model had HRs adjusted for social deprivation, ranging from 1.67 to 2.53 for quintile (Q) 2 though Q5 (Q5 being most walkable), with the highest HR being for Q3 (test for trend p=0.05). The HR (unadjusted) for baseline greenness was 0.96 for a 1-interquartile range increase (p=0.76), The HR for greenness averaged over 1982-2016 adjusted for social deprivation was 0.80 (p=0.07).

Conclusions: Although statistically non-significant, the magnitude and direction of TRAP HR was similar to previous studies. This study was the first study to our knowledge to assess whether walkability and greenness are associated with breast cancer risk. We found that those residing in less walkable communities; or in neighbourhoods with more greenness had lower risk of breast cancer (statistically non-significant). More research into these associations is warranted.

Lay summary

Breast cancer is the leading cause of cancer among women worldwide resulting in a large burden of illness. There are many breast cancer risk factors, including those that can and cannot be modified. When it comes to cancer prevention, modifiable risk factors are of particular interest. The urban environment is comprised of an understudied set of modifiable risk factors. This study used the British Columbia Generations Project cohort linked with the Canadian Urban Environmental Research Consortium dataset in attempts to analyse characteristics of the built environment as a risk factor for breast cancer in post-menopausal women in British Columbia. The study found increased breast cancer risk for residents living in areas with increased baseline and longitudinal traffic-related air pollution. Although these results were not significant, the magnitude of risk was similar to previous research. Decreased levels of longitudinal greenness and increased levels of walkability were associated with a decreased risk of breast cancer, both results were near significant. This research will provide insight for individuals, planners, and policy makers on how to identify and mitigate cancer risks. Further research in this field is warranted to fully understand the role different aspects of the built environment have on post-menopausal breast cancer risk.

Preface

This thesis received ethical approval from the University of British Columbia (UBC) Behavioral Research Ethics Board (REB) on March 27, 2020 in a Post Approval Activity (H20-00151). Data were drawn from the ongoing British Columbia Generations Project (BCGP).

The work presented in this thesis was conducted under the supervision of Dr. Trevor Dummer, with guidance from the supervisory committee: Dr. John Spinelli and Dr. Lawrence Frank. The literature review and statistical analyses were carried out by Sean Harrigan. The ethics application and data request were completed by Sean Harrigan. The study design was conceived and conducted by Sean Harrigan, with assistance from Dr. Dummer and Dr. Spinelli. Analysis was conducted by Sean Harrigan with guidance from committee members. Finally, the thesis writing was completed by Sean Harrigan, and reviewed by the committee members.

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List of abbreviations

BC	British Columbia
BCGP	British Columbia Generations Project
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 1
CANUE	Canadian Urban Environmental health Research Consortium
cm	Centimetre
DAG	Directed acyclic graph
DES	Diethylstilboestrol
DNA	Deoxyribose nucleic acid
ER	Estrogen receptor
FSA	Forward Sortation Area
HRT	Hormone replacement therapy
kg	Kilogram
LUR	Land use regression
NO_2	Nitrogen dioxide
NO_x	Nitrogen Oxides
PA	Physical activity
PAH	Polycyclic aromatic hydrocarbon
PM	Particulate matter
PPB	Parts per billion
PPV	Positive predictive value
PR	Progesterone receptor
SES	Socio-economic status
TRAP	Traffic-related air pollution
UFP	Ultrafine particles
US	United States
Veg	Vegetables
WHO	World Health Organization
α	Alpha
μm	Micrometer

Acknowledgements

Firstly, I would like to thank my supervisor, Dr. Trevor Dummer for all the support and guidance throughout the entire process. I would also like to thank my committee members Dr. John Spinelli for all of your advice and direction on the study design and statistical analysis, as well as Dr. Lawrence Frank, for your expertise on the urban environment.

I would also like to acknowledge UBC, CIHR and the Laurel Watters Fellowship for the financial support as well as the BC Generations Project research and data manager for access to the data.

Finally, I would like to thank my family and friends for all the motivation and support, as well as mi novia Valeria, muchas gracias! You have all been a huge inspiration to me throughout my life, thank you.

To,

Mom & Dad

Chapter 1: Background and objectives

1.1 Study Background

Breast cancer is the most common cancer in women worldwide and the leading cause of cancer deaths among women.[1–5] Breast cancer risk increases with age and lifetime exposure to estrogen, resulting in a doubling of breast cancer risk for post-menopausal women.[10] Other known risk factors include genetic mutations, family history, reproductive history, and lifestyle factors.[11] Research indicates that up to 50% of breast cancers are preventable and are due to environmental and behavioural factors, which may include air pollution and physical activity (PA), among others.[6] This underscores the importance of research into these risk factors, especially for post-menopausal women.

Characteristics associated with the built environment are important modifiable risk factors that can influence breast cancer risk.[12] Urban areas with increased traffic-related pollutants, such as nitrogen dioxide (NO_2), have been linked to increased risk of breast cancer.[11,13–16] Similarly, residential greenness and walkability are important urban characteristics. Greenness and access to green spaces is the surrounding level of vegetation or access to parks, woods, etc., whereas walkability is how conducive the environment is to using walking as a form of transport. Urban green space and walkability also have been shown to play a role in chronic disease, both directly and indirectly, but little research has been done in breast cancer specifically.[17–20] Importantly, these factors are also linked to important health risks, such as reduced PA and obesity, which are also associated with increased risk of developing breast cancer.[20–23]

1.2 Objectives and problem statement

In line with global trends, breast cancer is the most common cancer in women in British Columbia (BC), accounting for nearly 30% of cancer diagnoses and making it the most common cancer type among women.[24] This statistic outlines the importance for research into modifiable approaches to reduce the breast cancer burden in the province.

One set of understudied set of risk factors are characteristics of the built environment (both human-made and natural factors), specifically TRAP, greenness, and walkability. Assessment of the impact that the built environment has on breast cancer risk may play a key role in further reducing the burden on breast cancer. This study used a longitudinal cohort design to assess the relationship between breast cancer risk and three characteristics of the built environment.

The study utilized the British Columbia Generations Project (BCGP)[8] cohort and linked Canadian Urban Environmental health Research Consortium (CANUE)[9] datasets, specifically TRAP, walkability and greenness, to characterize the impact of specific features of the built environment as risk factors for breast cancer in post-menopausal women in BC.

The study objectives are:

1. Conduct a scoping review on how characteristics of the built environment (specifically, TRAP, urban walkability and residential greenness) affects breast cancer incidence in post-menopausal women.

2. Summarize the BCGP cohort in relation to TRAP (NO_2), walkability and residential greenness in relation to breast cancer cases and non-cancer participants.
3. Assess the association between TRAP, walkability and greenness and breast cancer risk

1.3 Rationale

This longitudinal analysis of built environment risk factors for breast cancer, with data on pre-diagnosis environmental exposures, provides an important addition to the literature. A direct association between TRAP has been observed in multiple observational studies, however some studies have not found conclusive results and many authors have indicated the need further research in the subject area to fully understand the association. Further, the literature assessing the association between breast cancer incidence and other aspects of the built environment (i.e., urban greenness and walkability) is very limited. This study is, to our knowledge, the first to assess the relationship between TRAP and breast cancer risk in the Lower Mainland of BC, as well as one of the first to investigate the relationship between greenness/walkability and breast cancer risk. This research may be able to provide insight for individuals, planners and policy makers on how to identify and mitigate risks and approaches to community design to lower breast cancer risk.

1.4 Ethical considerations

The study was approved by the UBC Behavioural Research Ethics Board (REB) and involves secondary data analysis of BCGP and linked CANUE data. BCGP has been created as a resource for researchers to examine the environmental, social, and genetic causes of chronic disease. Both research risk and participant vulnerability are low. Research risk was minimized in this study as all data were de-identified through the assignment of a unique study ID number to each participant.

All data that could allow identification of participants was been suppressed (including postal codes). Only de-identified data was provided to the study team.

1.5 Thesis outline

This thesis is divided in to five chapters, organised as follows. Chapter 1 sets out the foundation for the thesis, the research objectives and the rationale for the study. Chapter 2 provides background and presents the scoping review on breast cancer risk and the built environment**.** Chapter 3 describes the methodology. This includes the descriptions of study design, the sources of data, the study participants and the aspects of the built environment. The statistical analyses performed in this study are also described in detail Chapter 3. The results and findings are presented in Chapter 4. Finally, Chapter 5 presents the discussion and conclusions**.** This includes a focus on the implication of the study as well as the strengths, weaknesses and future recommendations.

Chapter 2: Background and scoping literature review

2.1 Breast cancer overview

2.1.1 Background and etiology

The human body is made up of trillions of cells. Cell growth and division makes up the natural cell lifecycle and results in the production of new cells.[25] When cells age or become damaged, they are programmed to die, in a process called apoptosis. However, when this process breaks down, the result is an uncontrolled group of cells. Cancer is the term used for a collection of diseases which involve cells in a part of the body to begin to divide without stopping.[25] Abnormal cancer cells continue to grow and divide even when they no longer function normally, or when new cells are not needed. This continuous growth and division can result in a mass of cells, called a tumour. Tumours can be either benign, premalignant or malignant. A benign tumour is localized and does not have the ability to spread to adjacent normal tissue, or to other parts of the body.[26,27] These types of tumours are not considered cancer. A premalignant tumours is a tumour which is not malignant, but has the possibility to become malignant in the future.[28] A malignant tumour (or cancer) is a tumour that has the capacity to spread to adjacent normal tumour and to other parts of the body. A malignant tumour that has not yet spread to adjacent normal tissue, it is called in situ. Once a tumour spreads to other body parts, other than lymph nodes close to the original tumour, it is termed a metastatic tumour. [26,27]

Staging of cancers is generally divided into four stages; however, these stages can vary by type of cancer. The most common type of staging for breast cancer is the TNM system – tumour (T), node (N) and metastasis (M).[29–31] Staging cancers can be a useful technique to describe how extensive the tumour in size, the number of lymph nodes near the tumour and the potential to spread.[29] Each

type of tumour, node and metastasis can be graded on a scale of 0 to 4.[29] Stage 0 represents in situ, non-invasive cancers. Stages 1 and 2 describe tumours that have spread only to adjacent normal tissue or nearby lymph nodes and is not very large. Stage 3 indicates a large tumour, with spread to numerous lymph nodes and to possibly the skin or chest wall. Finally, stage 4 represents when the cancer has metastasized to distant parts of the body, like the lungs, bones or brain.

Breast cancer originates in the breast. Although rare, breast cancer can also occur in men. Most often, breast cancer starts in the cells of the milk ducts, which are the tubes which transport milk from the mammary glands to the nipple.[32] This type of breast cancer is known as ductal carcinoma. Another common type of breast cancer is lobular carcinoma, which originates in the cells of the lobules. Breast lobules are groups of glands which produce milk.[32] Breast cancer is subdivided into five different subtypes which predict outcome.[33] These subtypes are based on the expression of hormone receptors; progesterone receptors (PR), estrogen receptors (ER), and the HER2 oncogene, which allow the cells to grow. Luminal A and B are ER/PR positive subtypes and have HER2 negative expressions. Luminal A is characterised by low-grade tumours that are generally slow growing, resulting in the best prognosis.[34] On the other hand, luminal B tumours grow slightly faster, resulting in a worse prognosis than luminal A. The third breast cancer subtype is called normal-like. This cancer is similar to luminal A and is characterised by hormone receptor positive and HER2 negative. Normal-like breast cancer generally has a good prognosis, albeit, slightly worse than luminal A. The final two subtypes are ER/PR negative. One subtype is characterised by very high expression of HER2.[33–35] This is called HER2 enriched and are generally faster growing than luminal cancers. This subtype has a worse prognosis than those previously mentioned but can be treated with targeted therapies. Finally, triple-negative, or basal like tumours,

are cancers with negative hormone receptors and negative HER2 oncogenes. This subtype is more common in African American women compared to women of European ancestry.[34]

2.1.2 Epidemiology

Breast cancer is the most common type of cancer globally among women and is the leading cause of cancer death in women.[36] The global incidence for breast cancer is estimated at about 1.5 million new cases, with approximately half a million annual deaths.[33] In the United States (US), the American Cancer Society estimates that 1 in 8 women will develop breast cancer in their lifetime.[37] Breast cancer has been thought of as being a disease most prevalent in high income countries (HIC). The highest rates of breast cancer are in North America and the Oceania, and the lowest are in Africa and Asia.[38] However, this statistic may be changing, as a 2008 GLOBOCAN report stated that almost 50% of breast cancer cases and 58% of breast cancer deaths are in low- and middle-income countries (LMIC).[39] Current data has shown decreases in the incidence of breast cancer in HIC, and an increase in incidence in LMIC.[36] Due to difference in quality of, and access to, healthcare around the world, the 5-year survival of breast cancer varies greatly. Coleman et al. found that survival varied from 80% or over in North America, Japan and some of Europe to 60% in middle-income countries and to below 40% in low-income countries.[40] The study attributed this variation in survival to lack of early detection programs, and delayed onset of treatment.

In BC, breast cancer accounted for nearly 30% of cancer diagnoses in women, making it the most common cancer among women.[24] In 2017 in BC, 3,655 women were diagnosed with breast cancer (age standardized incidence rate of 147.1 per 100,000) and 675 women died (age standardized mortality rate of 27.1 per 100,000). The BC Cancer Agency estimates that 97% of BC women who

are diagnosed with breast cancer are over the age of 40. The BC age-standardized relative 5-year survival rate is 82.3%. The age-standardized relative 1- and 3- year survival rates are 95.9% and 88.9%, respectively. The table below presents a breakdown of incidence and mortality for BC women in 2017.

Table 1: Age standardized incidence and mortality rates for breast cancer in BC in 2017

Age group	Number of incident cases	Number of deaths	Incidence rate*	Mortality rate*
0-19	0	0	0	0
20-39	155	10	23.9	1.8
40-59	1255	150	176.9	21.1
60-79	1745	315	338.1	61.0
80+	500	200	395.5	155.0
Total	**3655**	**670**	**147.1**	**27.1**

Source: BC cancer[24]
**Age standardized rates (per 100,000 women) – the standard population is BC women in 1970*

There are many known risk factors for developing breast cancer; broadly related to behaviours, external factors, pre-existing conditions or genetics.[41] Many of these risk factors are not modifiable, for example, biological sex is a key risk factor for breast cancer, as nearly all cases occur in females and only approximately 1% of breast cancer cases occur in males.[42] Other important non-modifiable risk factors include aging, genetic mutations, having dense breasts and family history of breast cancer.[43] Key genetic mutations that increase breast cancer risk are the set of breast cancer genes BRCA1 and BRCA2. These genes are tumour suppressor genes and play a normal role in controlling cell growth and preventing the development of cancer. Mutations in these genes result in a large increase in breast cancer risk, with up to 85% of individuals with these mutations developing breast cancer in their lifetime.[41] However, despite this large increase in risk, these mutations are still quite rare, and only affect about 1 in 500 individuals.[41,44] Family history

also plays an important role, relatives with a history of breast cancer and non-cancerous breast disease can increase the risk for breast cancer.[41] Ageing plays a pivotal role in risk as well. As with any cancer, as people age, telomeres shorten, and cells can begin to not reproduce normally. This leads to an increased risk and mortality associated with age.[3,45] Hormones and age at menstruation and menopause also play a key role in breast cancer risk. Earlier onset of menstrual periods and later onset of menopause expose women to hormones for longer periods of time, and thus increase breast cancer risk. A worldwide study found that for every one delayed year of menopause, breast cancer risk significantly increased by a factor of 1.03.[46] The age of first birth can also impact the risk of breast cancer, having children earlier and having more children reduce the risk of breast cancer.[47] Pregnancy can induce a change in hormones which lead to lower levels of bioavailable estradiol, a hormone which increase the risk of postmenopausal breast cancer.[48]

Despite many non-modifiable risks, up to 50% of breast cancers are preventable, and are due primarily to environmental and behavioural factors.[6] Some of these modifiable factors include alcohol consumption, night-shift work, obesity, physical inactivity, as well as urban environmental factors. Alcohol consumption has been consistently found to be associated with breast cancer risk. A large prospective cohort found that moderate levels of weekly alcohol consumption was associated with a statistically significant increase in risk.[49] The study also found binge drinking to be associated with increased risk. Earlier and later adult life drinking were found be associated independently. Obesity and PA can also influence breast cancer development; in fact, they not only increase the risk of breast cancer, but can also increase the risk of relative mortality.[22,50] Socio-economic deprivation is associated with a decreased risk of breast cancer.[51] Deprivation is the lack of social or material necessities in a society. It has been shown in many studies that breast cancer

rates are lower in areas that are more socio-economically deprived.[51,52] These associations between deprivation and breast cancer risk can be partly explained by the distribution of causal risk factors which vary between socio-economic statuses (SES), such as age at first birth and parity.[53,54] It has been found that women in more deprived neighbourhoods tend to have more children than those in less deprived ones. However, deprivation can also account for the confounding effect of community level SES, where SES is associated with both cancer and the features of the built environment.[55–57]

2.2 Measure of the built environment

Characteristics of the built environment can influence health risks, and in particular, breast cancer risk.[58,59] Some of these key characteristics of the built environment that may impact cancer risk include TRAP, urban walkability and residential greenness.

Over the past decades, increased urbanization and industrialization have released enormous amounts of hazardous chemicals into the atmosphere. Many of these pollutants are released by the combustion of fossil fuels in the form of carbon monoxide and dioxide, sulfur dioxide and nitrogen dioxide.[60] Unfortunately, many of these pollutants can cause serious health problems. The International Agency for Research on Cancer (IARC) has classified air pollution as a Group 1 carcinogen.[61] Group 1 indicates that there is significant evidence that the exposure is carcinogenic to humans.[62] In urban areas, vehicular emissions are the largest source of air pollution.[16] TRAP is a combination of toxic gases, including NO_2, carbon monoxide (CO), and volatile organic compounds, as well and fine particulate matter (PM). Many of these compounds, like carbonyls, metals, PM, volatile organic compounds and polycyclic aromatic hydrocarbons (PAHs) have

carcinogenic potential.[61] However, unlike other pollutants created by vehicles, NO_2 itself is not thought to be a carcinogen.[64,65] Despite this, fossil fuel combustion is the main cause of NO_2 release and variability in urban environments, making it a good marker for air pollution levels, and a proxy for other carcinogens like PAHs.[64–66] Because NO_2 is a good surrogate measure of TRAP, it is often used in many studies to assess TRAP exposure,[66] as it was in our study. Different metrics of TRAP can be proximity to major roads, traffic volume and density, vehicle exhaust emission density and pollution concentrations.[67] Pollution exposure and density estimates is often measured by collection samples as well as land use regression (LUR), dispersion, geostatistical and hybrid models.[11,59,67] Particulate matter is classified based on its diameter.[66] PM_{10} includes inhalable particles with a diameter that are smaller than 10 μm, $PM_{2.5}$ are inhalable particles less than 2 μm, finally ultrafine particles (UFPs) are any inhalable particle with a diameter less than 0.01 μm. Nitrogen dioxide and other gasses are often measured in parts per billion (ppb).

These pollution measures are generally provided for a given area or neighbourhood. However, the effect of pollution for a particular individual is dependent on a variety of factors. These include the amount of time spent outdoors, travel within a city, building and vehicle air exchange rates as well as breathing rates.[67] Unfortunately, it can be very difficult and expensive to collect individual exposure data cannot be collected due to high costs.

The built and natural environment also includes walkability and residential greenness. A community's walkability refers to the extent that the environment can influence the likelihood of walking as a mode of transport. Urban walkability can be measured by creating a walkability index using Geographic Information Systems (GIS). These indices use several components to assess

walkability, including residential density, street connectivity, land use mix as well as the retail floor space/area ratio.[68–70] Land use mix describes the degree to which functionally complementary activities (e.g. live, work, play) are co-located together. Land uses comprise a range of activities including residential, commercial, recreational, retail, institutional, industrial, etc.[71,72] Connectivity describes how well streets and neighbourhoods allow direct and efficient movement from one area to the next.

Urban green space typically refers to the presence of recreational open space, whereas greenness can refer to other forms of "green infrastructure" often centered on tree canopy. Green spaces can include features of the urban environment, such as parks, nature areas, roadside vegetation, roof gardens, and front and back yards.[73] There are many ways to measure urban green space, including numbers of parks, distance to parks. A common method to measure greenness is to use satellite images to distinguish different green space types and then calculate the number, the area, or the normalized difference vegetation index (NDVI) of urban greenness linked to participants' residential address.[73] The NDVI (used in this study as the indicator of greenness) is based on satellite measurement of the radiation reflected from the Earth's surface.[74] Through this, different features of the reflected spectra can be used to designate green spaces.

2.3 Built environment as risk factors for breast cancer – A scoping review

2.3.1 Scoping review outline and methodology

A scoping review was conducted on the impact of the built environment, specifically TRAP, walkability and green space, on breast cancer risk. A search of medical and public health databases, MEDLINE, EMBASE, PubMed and Google Scholar, was conducted. To review the effects of air

pollution three search terms, “breast cancer”, “post-menopausal” and “air pollution” were used in the databases’ search engines using the “AND” function. Likewise, the terms “breast cancer”, “post-menopausal”, “urban environment”, “walkability”, “physical activity” and “obesity” were used to search for these other environmental factors using “AND” and “OR” functions. In some search engines, walkability was not used as a search term as it was not an identified search term. Medical Subject Heading (MeSH) terms and the explode function were used to include associated keywords and subtopics, when available. Title and abstract reviews were conducted on studies which appeared relevant. Studies were included based on the criteria provided in the PECO (population, exposure, comparison, outcome) presented in Table 2. This review only considered traffic-related air pollutants; however, “traffic” was not added as a search term as the search results became too restrictive. Non traffic-related air pollutants were excluded at the PECO step under exposure. Since there was prior knowledge that the literature on the relationship between walkability and green space on cancer risk was limited, breast cancer mortality was also considered if no publications were found. In this case, the keyword “mortality” was added to the search. All study designs were included and there was no cut-off date use for inclusion. The search was conducted in May 2020 and was re-run in January 2021 to capture any new publications.

Table 2: PECO study inclusion criteria

PECO	Criteria
Population	Post-menopausal women
Exposure	1. Air pollution (concentrations of NO_2 or NO_x) 2. Walkability 3. Green space / greenness
Comparison	Not applicable
Outcome	Breast cancer*

Abbreviation: NO_2: Nitrogen dioxide; NO_X: Nitrous oxides
*In the case of no publications found for a particular aspect of the built environment, studies on breast cancer mortality may also be included.

2.3.2 Scoping review results

After review, 34 studies were selected according to the PECO criteria listed above. The included studies were broken down into study design and topic in the PRISMA diagram below (Figure 1). All studies were published after the year 2000, with 61% of them being published since 2015. The majority of the studies concerned TRAP. Some studies covered multiple topics. There were 14 cohorts, 9 case-controls, 8 reviews/meta-analyses and 3 cross-sectional studies. Of the 26 observational studies, 10 were conducted in the US, 7 in Canada, 5 in Europe and 2 in Asia. Of the air pollution studies, 15 studies reported on NO_2/NO_x exposure, 5 reported on particulate matter and 2 reported on ultrafine particles. Of the 17 studies which reported on air pollution, all but three found evidence to support that TRAP increases the risk of breast cancer in post-menopausal women. However, not all results were statistically significant, and many publications suggest the need for further research in the subject area, particularly in better measures of exposure and early life measures,[66] something our study was able to capture.

For walkability and green space, there was very limited research available. One study assessed urban walkability on breast cancer mortality and found that increased walkability was significantly associated with reduced breast cancer mortality.[19] Another study found that increased access to green space significantly reduced breast cancer risk.[18]

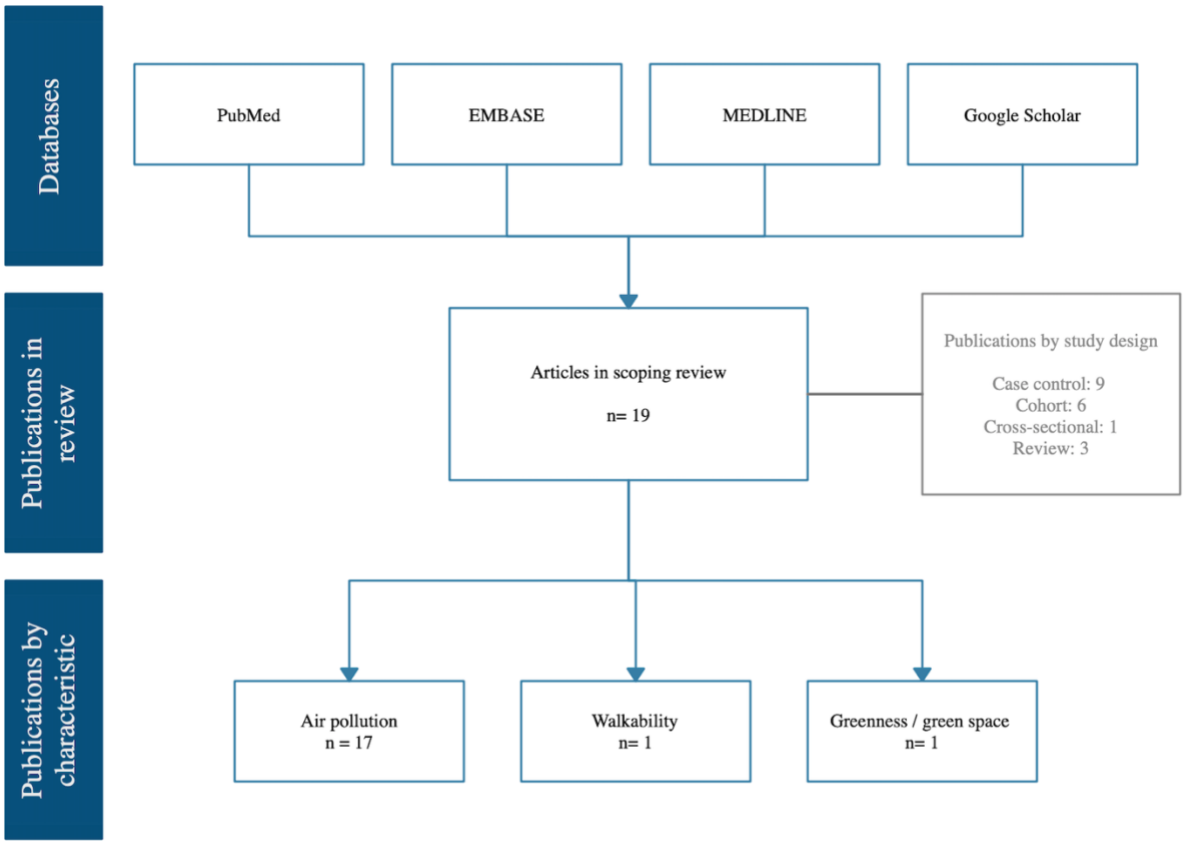

Figure 1: PRISMA diagram of publications in scoping review

Abbreviation: PA: physical activity
Note: Numbers of studies from each database was not recorded due to multiple overlapping studies. This PRISMA diagram only includes publications used in review, it does not include those used in introduction or discussion.

2.3.2.1 Traffic-related air pollution

TRAP has been studied in depth as a risk factor for lung cancer, but less so for breast cancer in post-menopausal women. Specific compounds formed by TRAP, PAHs, metals and benzene, can act as endocrine-disrupters and carcinogens.[66] PAHs are formed as a result of incomplete combustion of organic matter, like that of fossil fuel. Studies have shown these PAHs to be particularly important in breast cancer research as they have the capacity to bind to deoxyribose nucleic acids (DNA) to form DNA adducts (segment of DNA bound to a cancer causing chemical)

in breast tissue.[61,66] In addition to this, PAHs have been shown to induce breast tumour.[61,75] Both PAHs and metals produced in motor-vehicle combustion have been shown to have estrogenic properties, as well as produce oxidative stress, a key contributor to tumour formation.[66,76,77] Particulate matter, composed of small airborne particles as well as metals and hydrocarbons, has also been shown to be involved in carcinogenesis.[66,78,79]

Urban areas with increased motor vehicle pollution, such as NO_2, have been linked to increased risk of breast cancer.[11,13–16] Many observational studies have analyzed the association between TRAP and breast cancer incidence in post-menopausal women.[11,13–16] Most studies found evidence to support that TRAP increases the risk of breast cancer in post-menopausal women. However, not all results were statistically significant, and most publications suggested the need for further research in the subject area. Most studies used NO_2 to measure air pollution.[11,13–16] Two Canadian case-control studies demonstrated positive associations between NO_2 and breast cancer incidence.[11,16] In these case-control studies, Hystad et al. found an associated odds ratio (OR) of 1.10 per 10 parts per billion (ppb) increase in NO_2 in post-menopausal women. Crouse et al. concluded that for each increase of 5 ppb of NO_2, the adjusted OR was 1.31. A large multinational European cohort study assessed breast cancer in relation to multiple air pollution markers, including NO_2, NO_x and different measures of particulate matter.[59] This study, called ESCAPE, pooled results from pooled results from nine prospective European cohorts. The study found positive associations between most pollution measures and breast cancer incidence, however, only the association with NO_x was statistically significant. The large US based Sister's Study cohort looked at air pollution investigated the association between air pollution and breast cancer.[15] This

study did not find a significant increase in over breast cancer risk. The study did however find an increased risk for ER+/PR+ breast cancer in association with increased NO_2.

Particulate matter has also been studied in relation to breast cancer risk. A case-control study by Bonner et al. found that PM (total suspended particulate) was associated with a two-fold increase in the odds of breast cancer among post-menopausal women.[80] This study noted that there was not a significant association in pre-menopausal women. The Sister's Study did not measure a significant association between PM and breast cancer.[15] The same was found for the Nurse's Study II cohort, although the study suggested that proximity to major roads may be positively associated with increased risk.[81] The ESCAPE study determined that $PM_{2.5}$, PM_{10}, and PM_{coarse} (PM with diameter between 2.5 and 10 μm) were associated with elevated post-menopausal breast cancer risk.

In summary, the findings from the literature on air pollution and breast cancer vary. Most significant positive associations have been found between NO_2 and NO_x than PM. More research into the effects using longitudinal cohort evidence may therefore be beneficial.

2.3.2.2 Walkability and green space

Research into the direct association between breast cancer incidence in post-menopausal women and urban green space and walkability is very limited. No study was found on walkability and breast cancer risk; however, an Iranian study by Ghatar et al., [19] was found which investigated walkability and breast cancer mortality. Although the study was not specific to breast cancer risk, it was the only study investigating both breast cancer and walkability, it was therefore retained in

this scoping review. Ghatar analysed the relationship between urban walkability, car ownership and breast cancer deaths.[19] Interestingly, lower walkability was associated with higher rates of breast cancer mortality; while higher walkability was associated with lower rates of breast cancer mortality. Unfortunately, the entirety of this article was not in English, and therefore, only the abstract was reviewed.

Only one study was found assessing the effect of green space on breast cancer risk. A Spanish case-control study investigated the association between the residential proximity to green spaces and breast cancer risk.[18] The study indicated that the presence of urban green space (green space within 300m) was significantly associated with decreased breast cancer risk. The study had an estimated OR of 0.65 (95% CI = 0.49, 0.86) when adjusting for age, SES (at individual and area level), education and number of children. The study also observed a linear trend between the distance to urban green space and overall risk. This association accounted for multiple confounders and was not mediated by PA or levels of air pollution. The study noted the opposite effect in agricultural areas – the presence of green space was associated with an increased risk (OR = 1.33, 95% CI = 1.07, 1.65). Finally, the authors indicate that increased surrounding greenness (NDVI) to be associated with increased breast cancer risk (OR = 1.20, 95% CI = 1.07, 1.34).

Further research into the roles green space and walkability play on breast cancer risk is needed as there is a large gap in the literature. Longitudinal cohort analysis would allow relationship to be studied more in depth and provide a measure of temporality.

2.3.3 Scoping review conclusions

The scoping review uncovered multiple studies on the impact that TRAP, specifically NO_2, plays on breast cancer risk in women. The majority of studies found that increasing air pollution was associated with increasing breast cancer risk, although not all associations were statistically significant. Many studies presented the need for further research in the field. Only one study was found that linked walkability to breast cancer mortality and one that linked green space with breast cancer risk. For green space, the study found that an increase in green space was significantly associated with reduced breast cancer risk. The sole study for walkability observed that increased walkability was significantly associated with breast cancer mortality. Despite this limited research, a large body of evidence does link walkability and green space with physical activity and obesity which are known predictors of breast cancer.[82–85] That body of evidence and the few studies directly connecting with breast cancer risk with walkability and greenspace demonstrate a need for more research.

2.4 Obesity and PA: the indirect link between the built environment and breast cancer

The indirect link between the built environment and breast cancer, mediated through obesity and PA, was beyond the objective of the scoping review, however, this is an important element to consider.

Despite limited research in measuring the direct association of walkability and greenness with breast cancer risk, there has been more extensive research of the indirect association – through mediation by obesity and PA. Obesity and PA both are important risk factors for breast cancer, especially in post-menopausal women.[86–89] Most of the research documenting direct links between

walkability and green space and physical activity and obesity has been done in North America, Europe and Australia. An Australian study investigated the relationship between neighbourhood walkability and the walking behaviour of individuals residing in that neighbourhood.[90] The study controlled for covariates of SES, age, sex and gender. The investigators found strong positive associations between objectively assessed walkability of a neighbourhood and the amount of weekly walking by individuals. Recent findings indicate that cities with increased walkability, including distance walked, are associated with a decreased level of obesity.[20] Frank et al. found that the increase in mixed land use and daily distance walked was associated with a decrease in body mass index (BMI).[91] This same study found that each additional hour spent in a car was associated with a 6% increase and each additional hour spent walking a 5% reduction in obesity. Time spent in cars and walking was shown to be strongly related with walkability. An observational study compared neighbourhoods with high-walkability to those with low-walkability in San Diego.[84] The study concluded that residents in highly-walkable neighbourhood residents reported spending more time walking for errands or during school or work breaks. Residents of less-walkable areas had higher BMIs and greater rates of obesity than those residents in areas of high walkability. The presence of neighbourhood green spaces has been shown to significantly increase the amount of PA. Studies have shown that areas with more parks, outdoor recreational resources and better natural and environmental amenities have decreased BMI.[92]

The City of Vancouver has been working to support active transportation, forms of transportation that do not rely on an engine or motor. A study of the recently built Comox Corridor Greenway in downtown Vancouver (where planners reallocated road space to space for biking and walking) found that those living within 300 metres of the greenway were twice as likely to meet

recommended activity levels than those living further away.[93] Another recent study of Metro Vancouver, known as "Where Matters", compared obesity rates across levels of walkability and access to greenspace. This study employed a cross-sectional application of baseline data from BCGP. Results showed that those living in the walkable areas had a 43% less likelihood of being obese compared to those living in car dependent neighbourhoods and residents living with the maximum park access were also 43% less likely to have obesity compared to exurb resident counterparts.[94]

Chapter 3: Methods

3.1 Study design

In order to assess the breast cancer risk associated with three characteristics of the built environment, a prospective cohort analysis was used. This study used the BCGP, a prospective cohort which has been linked to CANUE urban environment data. This research took advantage of BCGP's longitudinal design, which enables the identification of individuals who develop breast cancer and other chronic diseases after enrollment (i.e., incident cases). Cox proportional hazards regression was used to assess time to event (breast cancer) in relation to urban environmental markers. Environmental markers – TRAP, walkability and greenness – were analysed for the study participants (cases and non-cases) to determine the role they play in breast cancer risk in BC Lower Mainland.

3.2 Study Population

3.2.1 Sources of data

3.2.1.1 British Columbia Generations Project

BCGP is BC's largest population health longitudinal cohort and is a regional cohort of the Canadian Partnership for Tomorrow's Health (CanPath, formerly CPTP), the Pan-Canadian prospective chronic disease cohort.[8] BCGP includes nearly 30,000 British Columbians aged 35-69 years. Initial data was collected from 2009-2016 using a health and lifestyle core questionnaire (HLQ).[95,96] BCGP participants completed one of two Health and Lifestyle questionnaires. Participants who enrolled from May 2009 to May 2010 completed the first version of the health and lifestyle questionnaire and medical history questionnaire, while participants who enrolled from

June 2010 to August 2016 completed the second version the questionnaire. BCGP collected baseline data on all participants on health, behaviour and lifestyle, residential history, occupation, diet and PA. The questionnaires collected a wide range of behavioural, socio-demographic, and health-related variables including age, marital status, education, employment status, annual household income, family health history and body measurements (height, weight, waist and hip circumferences). The majority of participants also provided baseline bio-samples (blood and urine) and other physical measures; however, these were not used in this study. Personal health history and past medical conditions were recorded. The international physical activity questionnaire short form (IPAQ-SF) was also used to collect PA data.[97] BCGP also collected information on lifestyle variables including tobacco use and exposure to second-hand smoke, alcohol use and physical activity and daily servings of fruits and vegetables. The follow-up of participants is ongoing through active recontact for additional questionnaire information. All participants also consented to passive follow-up via linkage to administrative health datasets, including the BC Cancer registry which was used to identify incident cancer diagnoses in this study.

3.2.1.2 CANUE

BCGP participants have been linked to the Canadian Urban Environmental Health Research Consortium (CANUE) datasets. CANUE is Canada's environmental data consortium which collects data on the built environment. The consortium generates geospatial environmental data, including information on air quality, pollution, weather and climate, greenspace and built environment characteristics such as walkability and deprivation.[98] CANUE data were linked to BCGP participants using two methods: (i) individual postal code level, based on the address at enrolment to BCGP, and (ii) historical individual postal codes to provide information on changes

over time. This linkage was done by Statistics Canada, which linked historic postal codes to CANUE datasets.

This project used three datasets from the CANUE database to characterize the built environment, relating to features that were hypothesized to be associated with breast cancer risk: 1. TRAP (NO_2); 2. Canadian Active Living Environments Index (CAN-ALE – an indicator of neighbourhood walkability); and 3. NDVI Landsat data (an indicator of greenness). These variables were chosen because they are generally representative of the built environment and they have been linked to different cancer and risk factors for breast cancer, such as obesity and physical activity.[66,91,99]

3.2.2 Setting of study: The Lower Mainland of BC

BC is the third most populous province, located on the west coast of Canada. The province is comprised of roughly five million residents, the majority of whom are of white European descent and between the ages of 15 and 64.[100]

The Lower Mainland is a region in BC which is located in the southwest corner of the province and is home to more than 60% of its residents. The Lower Mainland includes the City of Vancouver and the surrounding suburbs (Richmond, Burnaby, North and West Vancouver etc.), the northern coastal regions (Squamish, Lillooet, Whistler, etc.) as well as the Fraser Valley (Abbotsford, Chilliwack, Langley, Hope, etc.). In BC, of the 192 30-digit forward sortation area (FSA) postal codes, there are 108 of which fall in the Lower Mainland region. A map of the Lower Mainland region is presented in Figure 2, and is composed of the east-west region of Hope to Vancouver and north-south of Whistler to the Canadian-American border.

Figure 2: Map of Lower Mainland

Source: Apple Maps[101]

As of the 2016 Census, the Lower Mainland has a population of roughly 2.8 million. The majority of the population of the Lower Mainland is of white European descent (51.5%) followed by Asian descent (39.4%).[100,102,103]

Table 3: Ethnic makeup of the Lower Mainland

Ethnicity	Population	Percent of total
European	1,397,280	51.5%
East Asian	564,445	20.8%
South Asian	330,925	12.2%
Southeast Asian	173,060	6.4%
Aboriginal/First Nations	98,565	3.6%
Middle Eastern	63,300	2.3%
Latin American	36,855	1.4%
Black	32,325	1.2%
Other	43,295	1.6%
Total Population	**2,715,000**	**100.0%**

Source: Statistics Canada[100,102,103]

3.2.3 Inclusion and exclusion criteria

This study population included all women from the BCGP who were post-menopausal at enrollment or became post-menopausal during the follow-up period. Participants were recruited between 2009 and March 31, 2016. Breast cancer diagnosis was the primary outcome and was analysed across measures of the built environment. Cases were all women who developed post-menopausal breast cancers diagnosed since baseline recruitment who had completed the BCGP baseline questionnaire. A flow-chart of the results of the inclusion/exclusion process is outlined in Section 4.1.

The first exclusion criterion was whether participants resided in the Lower Mainland upon study entry. This area was selected to have comparable estimates of the built environmental variables, air pollution, walkability and greenness. This limited the study population to living in a more urban

environment as opposed to rural, where air pollution, walkability and greenness can all be more easily measured and compared. Determination of area residence was be done by cross-referencing the participant 3-digit FSA code to a list of FSA's in the Lower Mainland (see Table A1 in the Appendix). All participants who had an FSA at study entry listed outside of the Lower Mainland region were excluded from the study population.

Next, women with prevalent cancer diagnoses were excluded. It was important to exclude prevalent cancers because they can increase the risk for breast cancer.[104–107] Ricceri et al. have shown that women with a diagnosis of breast cancer have a 30% excess risk for secondary malignancies.[107] Treatment for prevalent cancers, like chemotherapy and radiation therapy have also been shown to increase the risk of secondary cancers.[108] By eliminating participants who had prevalent cancer diagnoses before study entry, the analysis was able to better identify risks related to aspects of the built environment, without the potential impact of factors related to the cancer treatment. Cancer history information was taken from the linked BC Cancer registry as well as the survey questionnaire. All individuals who had a prevalent cancer diagnosis before entering the study were excluded. This included all types of cancers, including prevalent breast cancer. Skin cancers, however, were not removed from the study because they are the most common cancers, and many such tumours can be benign.[109] Skin cancer is also mostly treated with surgery, therefore patients do not have the added risk of risk of primary breast cancer caused by chemotherapy or radiation treatment.[110]

Any participant who was not post-menopausal at some point in the study was excluded. Many occupational and environmental exposures have a higher risk in pre-menopausal women, however,

these tumours are rarer and often have specific aetiologies.[111] Post-menopausal women have many years of environmental exposures and therefore the built environment may have a larger impact. Post-menopausal breast cancers are also different from pre-menopausal ones as women have had exposure to different hormones throughout their lifetime.[10] Post-menopausal status was determined by self-identification in the questionnaire. The BCGP baseline questionnaire defined post-menopausal status as whether an individual's menstrual periods stopped for at least one year and did not restart (see Section 3.5.2.3 for more information). If the question was not answered, then the age at study entry was used. If the participant was 55 years or older, they were considered post-menopausal. The age of 55 is commonly used in studies for post-menopausal age if not otherwise indicated.[112] If the participant had indicated they were not post-menopausal and were over the age of 55 at study entry, then the age of 60 was used. Finally, if the participant was over 60, they were considered post-menopausal regardless of questionnaire. All person-years for participants who indicated they were post-menopausal women were included. Since the cohort followed participants over time, some women may have entered the study pre-menopausal but became menopausal during the follow up period. In that scenario, once the participant turned the age of 55 (or 60 years of age in the scenarios described above), person-years started to be accumulated towards the study. Women who were not post-menopausal at any point in the study were excluded.

Incident breast cancer diagnoses were identified through the BC Cancer Registry. Cases were defined as individuals diagnoses with all types of incident breast cancers, including those in situ as well as invasive cancers. Conversely, non-cases were defined as post-menopausal women who did not experience an incident breast cancer diagnosis. All participants with less than one year of

follow-up post study enrolment were excluded. For cases, this meant incident breast cancers diagnosed within one year of the study enrollment were excluded.

3.3 Data and variable cleaning

Data cleaning was done in R and Excel.[113,114] Categorical variables were grouped to created new variables for analytic purposes. In certain cases, continuous variables were converted into quintiles, categorical or binary variables. All entries which were coded as -9999, NA or blank were coded as NA.

3.4 Missing data

An analysis of missing data was done for each variable used in the models. Missing variable counts were provided along with the percent of total. For modeling purposes, complete case analysis was used.

3.5 Descriptive characteristics and bivariate analysis

An overall descriptive analysis of the study sample (including demographic, behavioural, social and health indicators) in relation to the environmental data (air pollution, walkability and greenness) was conducted for breast cancer cases as well as non-cases.

Descriptive statistics for categorical variables used counts and percentages and continuous variables were presented as means with standard deviations. Chi-square, t-tests and ANOVA tests were used to assess statistical differences between breast cancer cases and non-cases. An alpha of 0.05 was used to assess statistical significance. If data for certain variables did not appear to be

normal or did not meet specific criteria for the given parametric test, non-parametric tests were used. Visual statistics were also be provided in the form of boxplots plots and histograms, as well as in table format. Statistical analyses were also done to determine if built environment variables differed by these same key covariates using the same variables described above. Spearman correlations were also presented between all measures of the built environment to understand the relationship between these measures.

3.5.1 Study variables

Study variables are listed in Table 4. Each variable has multiple associated variables (e.g., categorical, binary, continuous). All of the following variables were considered for model building, the variable choice for modeling purposes will be describe in Section 3.6.2.

Table 4: Study variables

Built environment variables	**Other variables**
Greenness (NDVI)	Age
Baseline	Alcohol consumption
Average 1982-2016	BMI
Traffic-related air pollution (NO_2 in ppb)	Contraceptive use
Baseline	Education
Average 1980-2012	Ethnicity
Walkability	Fruit consumption
	Income
	Material deprivation
	Maternal breast cancer history
	Parity
	Physical activity
	Smoking
	Social deprivation
	Vegetable consumption

Abbreviations: BMI: body mass index; NDVI: normalized difference vegetation index; NO_2: nitrogen dioxide; ppb: parts per billion

A description of each variable is presented in the following sections. Descriptions of each variable were taken from BCGP and CANUE datasets.[8,9]

3.5.2 Participant health and personal baseline characteristics

3.5.2.1 Anthropometric measurements

Basic anthropometric include height measured in centimetres (feet and inches or cm), weight measured in kilograms (lbs or kg). Height was measured by standing with no shoes with back up against a wall while looking straight ahead. Weight was measured with using no or light clothing, ensuring the scale being properly zeroed. Waist and hip measurements were also taken and are used to determine certain obesity parameters. These were done in front of a mirror and were done by wrapping a measuring tool around the body so it cannot slide, but not tight enough that it indents the skin. The waist was found by placing thumb under the armpit and sliding down until reaching the hip bone. The hip was located by looking at one's profile and finding the largest point of the buttock. All anthropometric measurements were completed twice to ensure reliability. When BMI was not provided, weight and height were used to calculate the BMI (as described in Section 3.5.2.4).

3.5.2.2 Ethnicity

Ethnicity was determined by self-report. Participants were able to select all ethnicities that applied: Aboriginal, Arab, Black, East Asian, Jewish, Latin America/Hispanic, South Asian, Southeast Asian West Asian, White and other. From the listed ethnicities, a binary and a categorical variable was created. Since it was known that most of the participants were of white ethnicity, a binary

variable was created to represent those of white ethnicity and others. The reference category for modeling was white.

3.5.2.3 Women's health

Female health variables include number of births, contraceptive use and menopausal status. The number of births was recorded as a numerical variable and the contraceptive use was recorded as a binary variable (never and ever).

Menopausal status was defined as whether an individual's menstrual periods stopped for at least one year and did not restart. Participants were asked if they had gone through menopause and were able to indicate one of the following four answers:

1. Yes, natural menopause
2. Yes, other reasons (surgery, chemotherapy, medication)
3. No
4. Don't know

If the participant did not answer the menopausal status question in the survey, or they did not know, then an age cut off of 55 years was used to determine menopausal status (refer to Section 3.2.3 for more information).

3.5.2.4 Obesity

Obesity was measured using BMI, calculated by body weight (kg)/height $(m)^2$. BMI was self-reported by some participants and was measured and calculated directly for others. The following categorizations was used: BMI $\leq$18.5 as underweight, 18.5 to 25kg/m^2 as healthy weight, 25 to 30

as overweight, BMI ≥ 30 as obese.[115] The BMI variable was used as a continuous and categorical variable (underweight was used as the reference category). When measured BMI was unavailable, it was provided from self-report in the questionnaire.

3.5.2.5 Physical activity

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ short form). For evaluation of total physical activity, separate metabolic equivalent (MET) minutes per week (1 MET is defined as metabolic expenditure at rest) was calculated for moderate- and vigorous-intensive activities and walking activity according to the IPAQ scoring protocol.[116] The World Health Organization (WHO) recommends an equivalent of 6000 MET-minutes of moderate- and vigorous-intensity physical activity per week.[117] This cut-off was used as a binary variable to determine whether the participant met this recommendation of weekly PA (not meeting the recommendation was the reference category).

3.5.2.6 Smoking

Cigarette smoking and tobacco use was sub-divided into three categories: never-smoker, occasional smoker/past smoker and daily smoker. Never-smokers include individuals who had never smoked or smoked less than 100 cigarettes, and a past smoker was someone who had smoked more than 100 cigarettes but currently does not smoke. A binary variable was also created, with never-smoker or ever-smoker, using 100 cigarettes as the benchmark for an ever-smoker. Never-smoker was the reference category.

3.5.2.7 Alcohol consumption

Participants were asked about if they had ever consumed alcohol. For those that had, participants were then asked on average, how many times a week during the past year did they drink alcohol (categorical variable ranging from once a month to 6-7 times per week), as well as how many drinks they had in the past week (including the type: red wine, white wine, beer, liquor/spirits and other) and if participants drink during a typical weekend. A categorical variable for alcohol consumption was based on the frequency of drinks consumed. The categories were never, less than once per month, less than 1 time per week, 1-3 times per week and 4-7 times per week. A binary variable was also created to represent ever and never-drinkers. The number of drinks was based on the standard drink size of wine or wine cooler (142 mL, 5 ounces), bottle/can of beer (341 mL or 12 ounces) and straight alcohol or mixed drink (43 mL, 1.5 ounces). For both variables, never-drinkers were the reference category.

3.5.2.8 Diet

Dietary information was collected by asking questions about what the participant ate during the typical day. This included how many servings (1/2 cup or 125mL) of fruits, vegetables and 100% fruit/vegetable juices consumed during a typical day. The number of servings of fruits and for vegetables was recorded as a numerical variable as well as categorized as 0, 1 to 2, 3 to 4 and 5+ servings per day. Zero servings was used as the reference category for both fruits and vegetables.

3.5.2.9 Socioeconomic status

Socioeconomic status (SES) was recorded by the approximate total household income from all sources before taxes in the previous year. Income was categorised as <$50,000, $50,000-$100,000, $100,000-$150,000 and >$150,000. Less than $50,000 was used as the reference category.

3.5.2.10 Social and material deprivation

Deprivation scores have been developed to characterize communities in relation to material and social deprivation. Deprivation status was provided through CANUE and was linked to the postal code at study entry. Scores were measured for social and material deprivation and were measured by dissemination area number, dissemination area population, codes of each territory (provinces, Canadian regions, Census Metropolitan areas (CMAs), and geographic areas). This study used the regions variable. The variables were presented as quintiles, where is 1 was the least deprived and 5 was the most, with the lowest quintile being the reference category.

3.5.2.11 Education status

Education status was measured as a categorical variable. Individuals were grouped into the following five categories based on the highest level of education completed: not completed high school, high school, trade/ technical or vocation school, community college diploma, University certificate below Bachelor's degree level, Bachelor's degree, Graduate degree or none. The age of completion of the highest of education was collected. These categories were used to create a new categorical variable which represented the highest level of education completed. This resulted in

categories of high school or below, diploma/trade and University, where those who completed high school or below were the reference category.

3.5.3 The Built environment

3.5.3.1 Traffic-related air pollution

TRAP was measured using concentration of NO_2. This was measured as the average concentration in parts per billion (ppb) at time of study entry.[118] A variable was also created to represent the average concentration of NO_2 over the period of 1980 to 2012.

3.5.3.2 Walkability

The Canadian Active Living Environments (Can-ALE) Index was used as the indicator of walkability.[98] The Can-ALE dataset provides a set of Geographic Information Systems (GIS) measures of walkability. The ALE Index is the sum of the z-scores for each Can-ALE measure available throughout Canada for that census year. This includes intersection density and dwelling density for 2006 and intersection density, dwelling density, and points of interest for 2016. Walkability scores were measured in 2006 and 2016 and were extrapolated for the subsequent years. These two scales were not translatable, as they used different measurement and scoring system.

The 2006 scale was chosen because it was an earlier time period and a representation of long-term exposure to measure the latency of breast cancer. The summed z-scores therefore indicates the distribution of the Can-ALE measure values for each dissemination area (DA) relative to all DAs in Canada. This means that a negative Can-ALE index scores indicate below average ALE

measures and positive ALE index scores indicate above average Can-ALE measures. A z-score near zero indicates that the DA is near the Canadian average for the quality of the active living environment. The Can-ALE was also divided into quintiles to produce a categorical variable. This quintile variable was specific to the Lower Mainland, as opposed to the z-score, which was generated for Canada as a whole. Quintile 1 represented the least walkable areas and quintile 5 represented the most walkable. Quintile 1 was used as the reference category. This quintile variable was also converted to a trend variable for multivariable regression analysis. The Can-ALE score was taken for the participant at their residence at study enrolment.

3.5.3.3 Residential greenness

Greenness was measured by the Normalized Difference Vegetation Index (NDVI). CANUE has compiled a complete set of NDVI data covering all of Canada since 1980. In this study greenness was measured as the annual mean NDVI by postal code FSA. The NDVI is calculated by the difference between the near infrared wavelength (NIR) reflectance and the red wavelength reflectance (RED) and dividing this value by the sum of these two intensities.

Equation 1: Normalized Difference Vegetation Index

$$NDVI = \frac{NIR - RED}{NIR + RED}$$

Abbreviations: NIR: Near infrared wavelength; NDVI: normalized difference vegetation index; RED: red wavelength

NDVI is a measure of vegetation health. Chlorophyll is a health indicator, and strongly absorbs visible light.[119] Because of this, healthier and dense vegetation will result in a higher NDVI score. The NDVI results in a value between -1.0 and +1.0, where -1.0 indicates the presence of no

vegetation and 1.0 indicates dense health vegetation. The greenness variable was also converted into tertile categorical variable for analysis as NDVI can vary from slightly year to year due to rainfall and other conditions. Tertiles was chosen as it was used in other greenness health-related studies.[120] Tertile 1 was used as the reference category. Creating tertiles minimized the effect of yearly differences. The NDVI score was taken for the participant at their residence at study enrolment and a variable for the longitudinal average was calculated between the years of 1982 to 2016.

3.6 Multivariable analysis

This study used multivariable Cox proportional hazards (PH) modelling. Separate Cox PH regression models were made for each of the following built environment variables: TRAP (baseline NO_2 and average NO_2 over the period of 1980 – 2012), walkability (ALE-index) and greenness (baseline NDVI and average NDVI over the period of 1982 – 2016). Models were created for each built environment variable. Fully adjusted models included all variables presented in the section above, while final models were constructed for each built environment variable. Final models were determined using the change-in-estimate model building process presented in Section 3.6.2. Hazard ratios (HRs), 95% confidence intervals (CIs), p-values (p), concordance and Schoenfeld's test (see Section 3.6.2) were provided for each model. Test for trend p-values were calculated for categorical quintile variables for the built environment – walkability and greenness. This was done by converting the quintile factors to a numeric variable (low quintile = 1, lower-middle quintile = 2, middle = 3, upper-middle = 4, and high quintile = 5).

3.6.1 Cox proportional hazards regression

Cox PH is a regression modeling technique often used in survival analysis as it factors in person-time into the model. The outcome variable was breast cancer, and the explanatory variables were the three environmental factors. The outcome variable was either a breast cancer diagnosis (coded as 1) or a breast cancer-free at the date of last follow-up (August 1st, 2019) or censoring (coded as a 0). In this study, censoring was defined as death. Data on diagnosis of other incident cancers was not collected, so these participants were not censored. Time was recorded as a continuous numeric variable, measured in years.

Cox PH regression models the relationship multiple predictor variables and a binary outcome variable. In a Cox model, the measure of effect is known as the hazard rate, which is defined as the risk of an event in the next small time interval (incident breast cancer diagnosis), given the participant has survived up to the given time.[121] Therefore, the cumulative hazard is the number of events per unit time. The model takes on the following equation:

Equation 2: Cox regression equation

$$h(t, X) = h_o(t) \cdot e^{B_1 x_1 + B_2 x_2 + \cdots + B_k x_k}$$

In this equation, X denotes the predictor variables x_1, x_2, …,. B_1, B_2, … denote the effect size of the corresponding predictor variable, and h(*t*,X) denotes the hazard at time t given covariates x_1, x_2, …. The baseline hazard $h_o(t)$ is the hazard at time *t* when all the predictor variables are equal to zero. The values B_1, B_2, ... are estimated by maximum likelihood giving estimates b_1, b_2, ... as presented in the equation above. Similarly, the baseline hazard is estimated, giving an estimate of h(*t*,X).

The hazard rate can be thought of as the probability that if the event (breast cancer diagnosis) has not already occurred, that it will occur in the next time interval, divided by the length of that time interval. This time interval is made infinitesimally small, so the hazard rate represents an instantaneous rate.[121] The hazard ratio (HR) for a binary variable is defined by the hazard rate when that variable when equal to 1, divided by the variable when equal to zero with the value of all other variables remaining the same. For a continuous variable, the hazard ratio is calculated by dividing the hazard rate for when the variable is 1-unit greater by the hazard rate for the same variable 1 unit less, with all the other variables remaining the same. For example, this could represent the change in risk for developing breast cancer for white females compared to "other" females, if white females are coded as "1" and other females are coded as "0". In the context of this study, the interpretation of the hazard ratio is the relative risk of developing breast cancer at any given time between units of the of the predictor variable. For example, it is the relative risk of developing breast cancer if the continuous variable in question, for example age, rises by 1 unit.[122] After estimating the b_1, b_2, ..., the hazard ratio of the i^{th} variable is calculated by $\exp(b_i)$.

Cox regression is a semi-parametric regression, and therefore does not assume a distributional shape for the baseline hazard. The assumptions for a cox model are as follows:

1. Non-informative censoring
2. The observations are independent
3. Hazards are proportional – hazard ratio is constant over time

Non-informative censoring occurs when participants drop out of the study for reasons which are unrelated to the study.[123]

3.6.2 Model building approach

For each of the three built environment variables, a similar model building strategy was used. The outcome variable in all three models was post-menopausal breast cancer diagnosis. This was binary variable recorded as either a 1 for breast cancer cases or a 0 for non-cases. The primary explanatory variable was the built environmental variable (TRAP, walkability or greenness). Two models were built for air pollution: one for the baseline NO_2 measurement and one for the average air pollution between the years of 1980 – 2012. Similarly, two models were also made for greenness, one for the baseline NDVI measurement and one for the average NDVI over the years of 1982 – 2016. Both air pollution and greenness were measured as continuous numerical variables. For these continuous variables, the HR indicated the increase in risk for an *x*-unit increase in air pollution or greenness. Walkability was measured as a quintile categorical variable. A categorical variable was chosen as to provide a more intuitive interpretation of the hazard ratio, as the walkability variable was given as a z-score. The HR for a specific level of the categorical variable indicated the risk compared to the first quintile. Note that in the models, the p-value for categorical variables will be presented as a test for trend p-value. This was done by modeling the categorical variables as trend variables. Next, the walkability categorical variable was be used and the HR for each quintile compared to the first quintile will be reported. This model used the same covariates as determined in the change-in-estimate trend variable modeling procedure.

The change-in-estimate method was used for model building. The aim of this method is to reduce confounding by retaining only the covariates which significantly change the HR. For the change-in-estimate procedure, all relevant potential covariates were determined a priori (Section 3.5.2). These variables were discussed in previous sections and have been found to be related to post-

menopausal breast cancer in other studies.[11,16,41,124] These variables were: age, alcohol, birth, BMI, contraceptives use, education, ethnicity, fruit consumption, income, material deprivation, maternal breast cancer history, PA, smoke, social deprivation, vegetable consumption. All 15 potential covariates listed above were then included in each of the five built environment models to create fully adjusted models. From there, one covariate was individually removed from the fully adjusted model to create 15 new models with 14 covariates each. The HR for the built environment variable was then compared to that of the fully adjusted model. A percent change in HR was calculated for each of the 14 models, and the model which had the smallest (closest to 0) was noted. The removal of this specific covariate was determined to not significantly bias the HR and was removed from the process. This step was repeated with the now 14 potential confounders and again, each variable was removed one at a time – comparing the resulting HR back to the fully adjusted HR through percent change. The final adjusted model was selected once the removal of each remaining variable resulted in a percent change of greater than 5%. A 5% change was chosen to ensure residual bias was small. For numerical built environmental variables (air pollution and greenness), the percent change depends on the definition of the unit increase for the estimation of the HR. For example, using 10-unit increase in ppb for air pollution resulted in larger percent changes than when using a 5-unit increase. For air pollution a 10 ppb increase was used and a 1-unit interquartile range (IQR) for greenness.

Once a final model was chosen, the PH assumption was examined, using the Schoenfeld's test. This test returns a p-value for each variable in the model, as well as a global p-value for the whole model. In the Schoenfeld's test, the null hypothesis is that the PH assumption is met, therefore a p-value less than 0.05 indicates the PH assumption is not met. In this case, a cut-off time-dependent

covariate would be added to the models. To determine the cut-off point, a plot of the Schoenfeld residuals against time to give an estimate time estimate of when the PH assumption was not met. If all p-values for the Schoenfeld's test were greater than 0.05, the assumption of proportional hazards was accepted, and the final model was kept. Finally, concordance was measured to produce an estimate of model fit. The concordance is a measure of goodness of fit and is equal to 0.50 when the model is making random guesses for survival.

3.7 Statistical software

The core data analysis was conducted using R 3.5.0 (R Core Team, Vienna).[113] This included all modeling, statistical tests, as well as visual statistics. Microsoft Excel was also used to clean data and create plots and figures.[114]

Chapter 4: Results

4.1 Study population

The BCGP has collected data on nearly 30,000 participants.[8] Of this, 69% are female and 21% are male. The age distribution consists of 13.3% of participants being between 35–44 years, 27.1% 45–54 years, 40.5% 55–64 years and 19.1% 65 years or older. There were 83.5% who stated they were of white European descent. The population was mostly well educated, married and either never smoked or a former smoker.

In total there were 20,071 female participants in BCGP. Of these female participants, 11,086 (55.2%) reported living in the Lower Mainland at the time of study enrolment. Of these participants, 1,333 participants had prevalent cancers (excluding skin cancer). This left 9,753 participants with no prior cancer history. Next menopausal status was assessed. Of the remaining participants, 2,111 did not reach menopause during their follow-up and were excluding, leaving 7,642 participants. Finally, those with less than 1-year of follow-up time were also excluded from the study, resulting in a final study population of 7,330 participants, see PRISMA diagram, Figure 3. There were 122 (1.7%) incident breast cancer diagnoses during follow-up time and 7,208 non-cases without a breast cancer diagnosis.

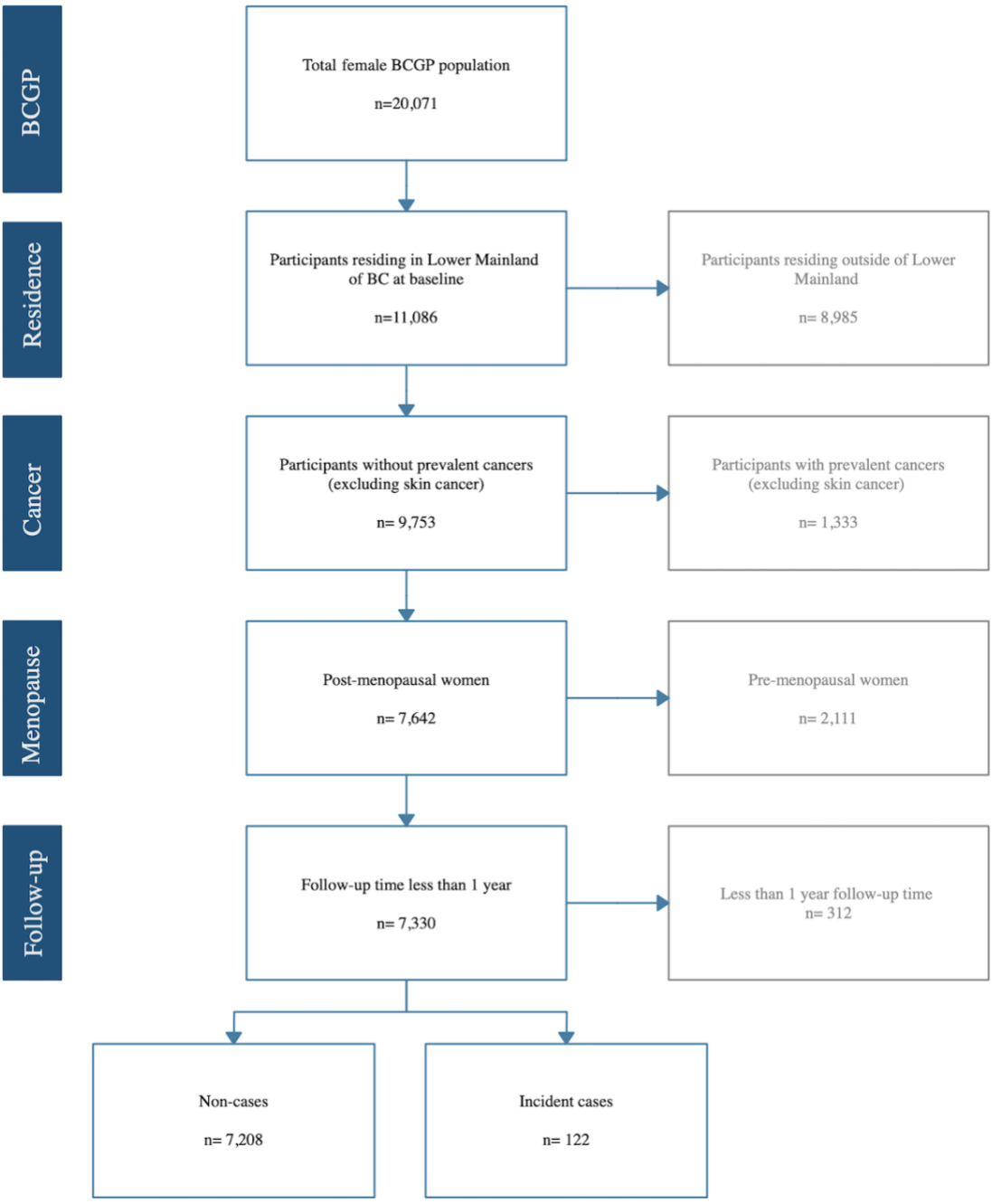

Figure 3: PRISMA diagram of study population

Abbreviations: BC: British Columbia; BCGP: British Columbia Generations Project

4.2 Missing data

Counts of missing data and relative percentages of the overall study population are presented in Table 5. The percentage of missing values for each variable of interest was relatively low. The variable with the most missing values was BMI at 14%. The remaining variables all had missing values under 10%. Age, maternal history of breast cancer and ethnicity all had no missing values.

Table 5: Missing values for variables of study

Variables		**Count of missing values**	**Percent of total population**
Built environment variables			
Air pollution (ppb NO_2)	BL	15	0%
	Average 1980 - 2012	15	0%
Walkability (ALE-index)	BL	489	7%
Greenness (NDVI)	BL	418	6%
	Average 1982 - 2018	7	0%
Other variables			
Age		0	0%
Alcohol consumption		46	1%
Birth		409	6%
BMI		986	14%
Contraceptive use		47	1%
Education		48	1%
Ethnicity		0	0%
Deprivation score	Material	935	13%
	Social	935	13%
Diet	Veg. servings	91	1%
	Fruit servings	85	1%
Income		572	8%
Maternal history of breast cancer		0	0%
PA		541	8%
Smoking		95	1%

Abbreviations: BL: baseline; BMI: body mass index; NDVI: normalized difference vegetation index; NO_2: nitrogen dioxide; PA: physical activity; ppb: parts per billion; Veg.: vegetable

4.3 Descriptive characteristics and bivariable analysis

The final study population consisted of 122 cases and 7,208 non-cases, for a total of 7,330 participants. Overall baseline characteristics are presented in Table 6. The average age at baseline was 58 years, with a SD of 6.3 years. The median follow-up time for non-cases was 7.2 years (min = 1.0, max = 10.4). The population was predominantly white (84%), the majority of the remaining participants were of Asian descent. The average BMI of the study population was 25.7 (SD = 5.3), which is considered to be overweight. Of the participants with a reported BMI, 2% were considered underweight, 45% were healthy weight, 20% were overweight and 30% were obese. Alcohol consumption was common, with only 6% never having consumed alcohol – the majority of participants drank more than 1 alcoholic beverage per week (55%). Cigarette smoking was quite rare, with only 3% of participants being current daily smokers. The average PA per week was measured to be 18.6 MET-minutes per hour, which does not meet the PA guideline outlined in Section 3.5.2.5. The SD for PA was large (15.3) – some participants did not exercise at all whereas others exercised a lot. The study population was well educated, with 41% having a University degree (16% of which had a Graduate degree). Most participants had an annual family income between $50,000 – $100,000 (36%), followed by <$50,000 at 23%. Measures for the built environment, including air pollution, walkability and greenness, will be described in further detail in the following sections.

Table 6: Baseline participant demographics

Variables		Overall		Case		Non-cases		p
		n or mean	% or SD	n or mean	% or SD	n or mean	% or SD	
Number of participants		7330	100%	122	2%	7208	98%	
Follow-up time (years)		7.4	2.3	4.4	2.1	7.5	0.6	<0.01
Age at baseline		58.0	6.3	60.6	5.58	58.0	4.82	<0.01
Alcohol consumption	Never	473	6%	10	8%	463	6%	0.70
	Less than 1 time per week	2419	33%	38	31%	2381	33%	
	More than 1 time per week	4058	55%	71	58%	3987	55%	
	Not reported	380	5%	3	2%	377	5%	
Birth		1.7	1.2	1.6	1.13	1.7	0.16	0.35
BMI		25.7	5.3	25.8	5.43	25.7	2.02	0.88
Contraceptive use	Ever	6436	88%	106	87%	6330	88%	0.61
	Never	847	12%	16	13%	831	12%	
Education	High school or none	0	0%	0	0%	0	0%	0.04
	Trade or Diploma	2772	38%	50	41%	2722	38%	
	Bachelor's Degree	1803	25%	24	20%	1779	25%	
	Graduate Degree	1185	16%	12	10%	1173	16%	
	Not reported	48	1%	1	1%	47	1%	
Ethnicity	White	6180	84%	106	87%	6074	84%	0.51
	Other	1150	16%	16	10%	1134	18%	
Deprivation score	Material	2.2	1.4	2.1	1.40	2.2	0.20	
	Social	2.8	1.6	2.5	1.59	2.8	0.25	
Diet	Fruit servings per day	2.5	1.6	2.6	2.03	2.5	0.24	0.53
	Veg. servings per day	3.3	2.1	3.5	2.65	3.3	0.32	0.30
Income	<$50,000	1700	23%	33	27%	1667	23%	0.17
	$50,000 - $100,000	2605	36%	49	40%	2556	35%	
	$100,000 - $150,000	1343	18%	15	12%	1328	18%	
	$150,000 +	1110	15%	14	11%	1096	15%	
	Not reported	572	8%	11	9%	561	8%	
Maternal breast cancer history		614.0	8%	19.0	16%	595.0	8%	0.01
PA	Total PA in MET-minutes per day	445.94	366.64	483.79	418.37	445.30	45.90	0.33
Smoking	<100 lifetime/ Never	3938	54%	61	50%	3877	54%	0.34

Variables	Overall		Case		Non-cases		p
	n or mean	% or SD	n or mean	% or SD	n or mean	% or SD	
Past smoker	2931	40%	57	47%	2874	40%	
Occasional smoker	99	1%	0	0%	99	1%	
Current daily smoker	256	3%	4	3%	252	3%	
Not reported	106	1%	0	0%	106	1%	

Abbreviations: BMI: body mass index; MET: metabolic equivalent time; p: p-value; PA: physical activity; SD: standard deviation Veg.: vegetable

None of the study variables: alcohol consumption, birth, BMI, contraceptive use, ethnicity, material or social deprivation, fruit or vegetable consupmtion, income, PA and smoking were signifcantly different between cases and non-cases. Conversely, age, education status and maternal history of breast cancer were significantly different betweeen cases and non-cases values (p = <0.01, 0.04 and 0.01, respectivley). Cases were on average two years older than non-cases (average age = 60.6 and 58.0, respectively). The study population was very well educated, with 41% having a University degree. History of breast cancer in cases was double that in cases compared to non-cases (16% and 8% respectively).

4.3.1 The built environment

The following section outlines the three measures of the built environment for the study participants. The average baseline air pollution was 12.9 ppb and 12.8 ppb for cases and non-cases, respectively (

Table *7*). A greater average yearly pollution concentration was seen, with 19.0 and 17.9 ppb for cases and non-cases. The average z-score was 1.1 and 1.0 for cases and non-cases. For modeling purposes, the quintile variable was used. Finally, the baseline and annual mean between the years 1982 and 2016 for residential greenness for both cases and non-cases was 0.3.

Table 7: Built environment characteristics

Variables		Overall		Case		Non-cases	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Air pollution	Annual average NO_2 ppb at BL	12.8	4.5	12.9	4.32	12.8	1.08
	Average for 1980-2012 (NO_2 ppb)	17.9	5.3	18.0	5.16	17.9	1.54
Walkability	BL	1.0	2.1	1.1	2.04	1.0	0.19
Greenness	Annual mean NDVI at postal code at BL	0.3	0.1	0.3	0.14	0.3	0.03
	Average for 1982-2016 (NDVI)	0.3	0.1	0.3	0.10	0.3	0.03

Abbreviations: BL: baseline mass; NDVI: normalized difference vegetation index; NO_2: nitrogen dioxide; ppb: parts per billion; SD: deviation Veg.: vegetable

4.3.1.1 Traffic-related air pollution (NO_2)

Nitrogen dioxide was used as a marker for TRAP and was measured in parts per billion (ppb). The overall mean ppb for NO_2 at baseline was 12.78 with an SD of 4.54 (Figure 4). The minimum NO_2 concentration at baseline was 1.4 ppb and the maximum was 34.3 ppb. When stratifying by cases and non-cases, the mean ppb at baseline was 12.9 (SD = 4.32) and 12.8 (SD =1.08), respectively (Figure 4). This difference in air pollution concentration between cases and non-cases was not significantly different (p = 0.69). Finally, the coefficient of variation for NO_2 was 35.5%.

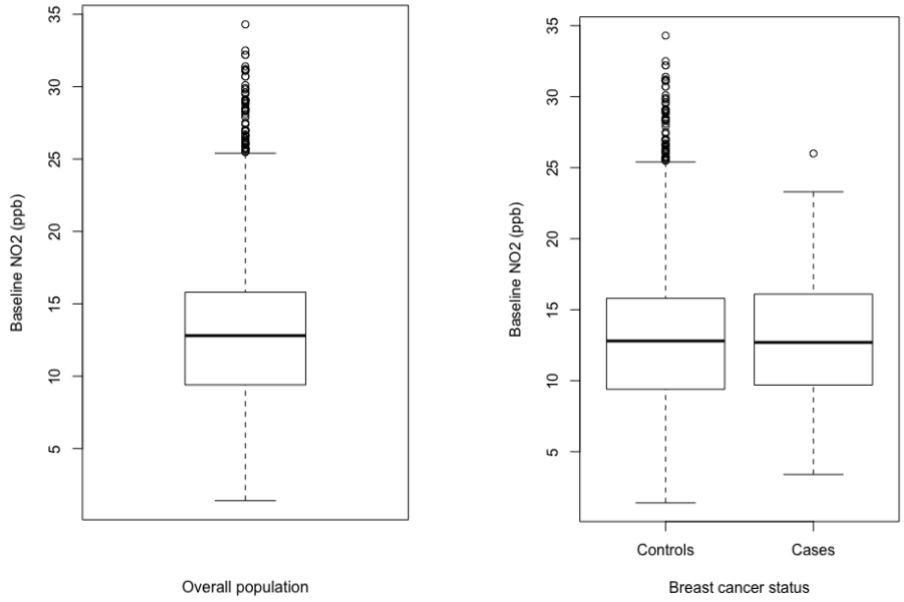

Figure 4: Baseline air pollution (ppb NO_2) for breast cancer cases and non-cases

Abbreviations: NO_2: Nitrogen dioxide; ppb: parts per billion

The average for the population between time period of 1980 – 2012 was 17.9 ppb (SD = 5.30); 18.0 ppb (SD = 5.16) for cases and 17.9 ppb (SD = 1.54) for non-cases (Figure 5). Similar to the baseline measurement, the longitudinal NO_2 concentration difference between cases and non-cases was not significant (p = 0.80). The minimum concentration was 1.49 ppb, and the maximum was 43.99 ppb. The coefficient of variation for the mean NO_2 concentration over the period of 1980 – 2012 was less than that of NO_2 at baseline, at 29.8%.

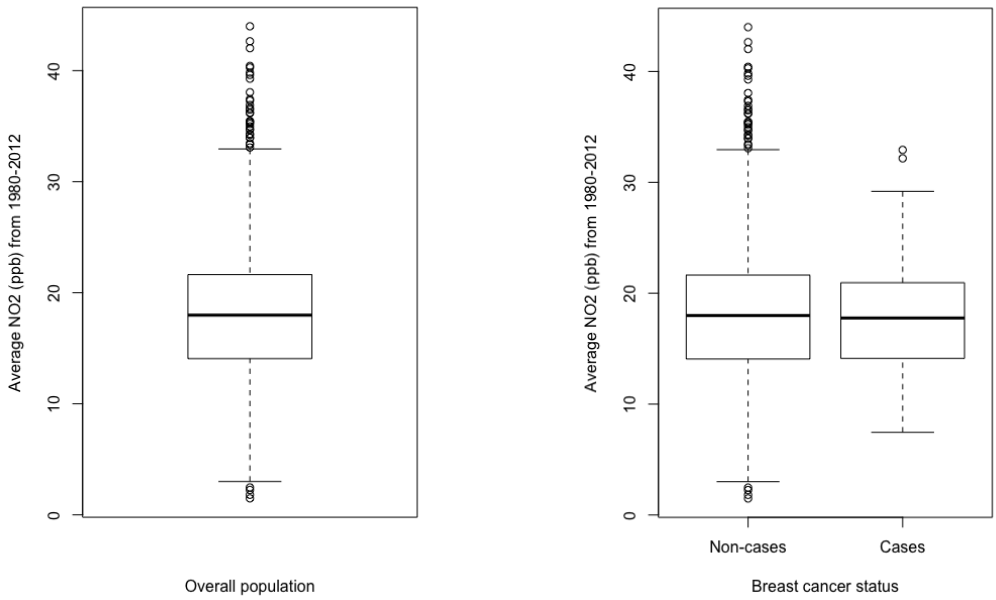

Figure 5: Average air pollution (NO_2) for cases and non-cases between 1980-2012

Abbreviations: NO_2: Nitrogen dioxide; ppb: parts per billion

4.3.1.2 Walkability

Walkability was measured using the 2006 ALE-index from the CANUE dataset. This dataset used z-scores to compare the walkability data across the entire country. The average walkability z-score was 1.00 (SD = 2.1), for cases was 1.10 (SD = 2.01) and non-cases was 1.00 (SD = 0.19) – this difference was non-significant (p = 0.57). Boxplots are presented in Figure 6, all distributions are right-skewed.

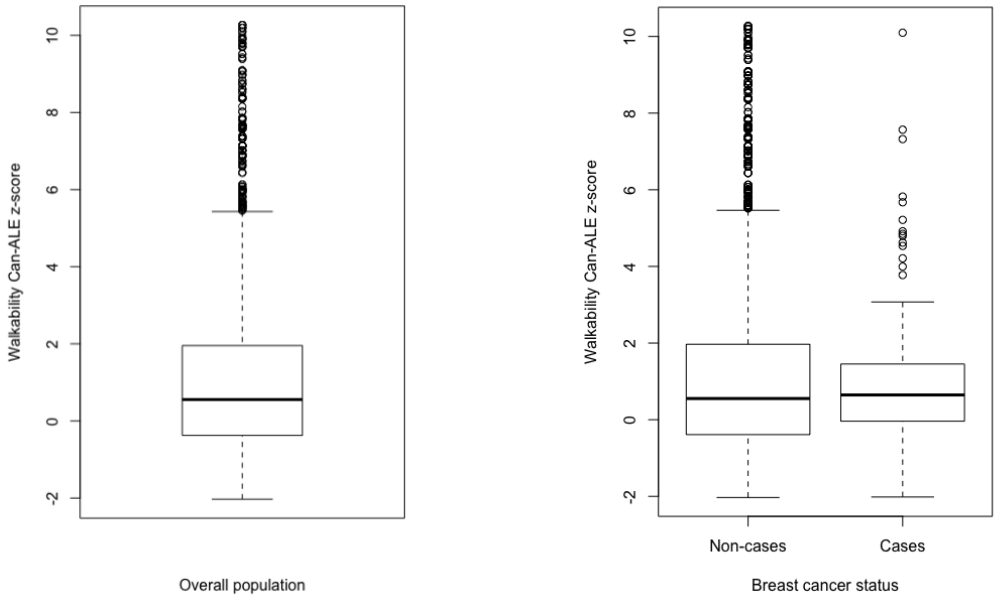

Figure 6: Walkability z-scores for breast cancer cases and non-cases

For the Cox modeling analysis, the variable was also divided into quintiles. This resulted in an equal distribution of non-cases, across each quintile. For breast cancer cases, 12%, 19%, 27% 23% and 18% of participants were in quintile 1 though 5, respectively.

4.3.1.3 Greenness

Greenness was measured using taking the mean annual NDVI at the site of baseline residence for the given year of entry. Figure 7 depicts boxplots of baseline NDVI for the overall population as well as stratified by cases and non-cases. The overall average NDVI at baseline was 0.34 (SD = 0.13) – cases had an average of 0.33 (SD = 0.14) and non-cases with an average of 0.34 (SD = 0.03). This difference was not significant (p = 0.70). The coefficient of variation for baseline NDVI was 36.6%. Similar to the other built environment variables, the non-cases had a larger SDs

compared to the cases, as well as more outliers, However, unlike walkability and air pollution, the distribution of greenness was not skewed.

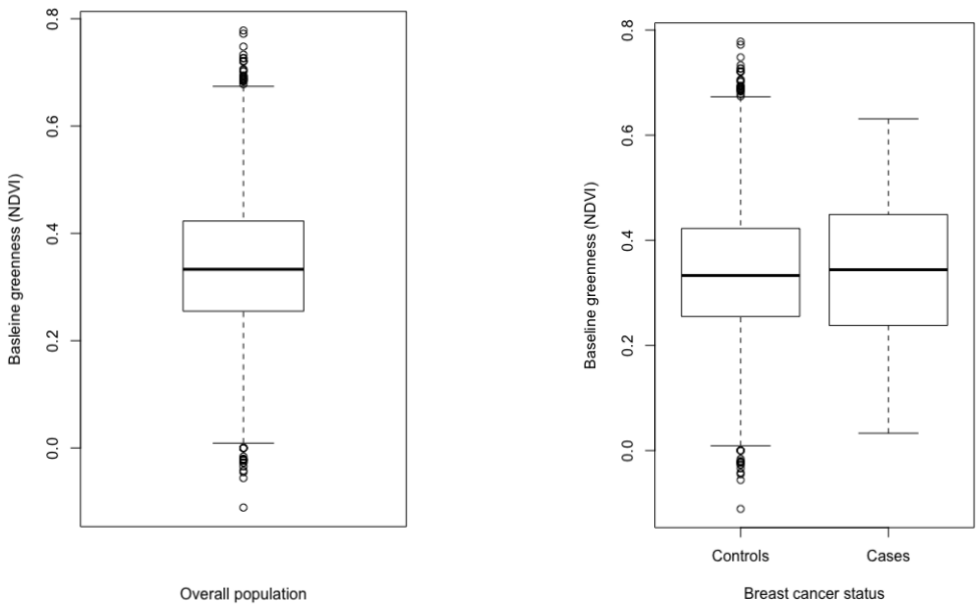

Figure 7: Baseline greenness (NDVI) for cases and non-cases

A variable for the average greenness NDVI over the time period of 1982 – 2016 was created. The average for the population was 0.34 (SD = 0.09); 0.34 (SD = 0.10) for cases and 0.34 (SD = 0.03) for non-cases, as presented in Figure 8. The minimum was -0.022 and the maximum was 0.73. The coefficient of variation for the mean greenness NDVI was 25.9%, which was smaller than the coefficient of variation for the NDVI at baseline.

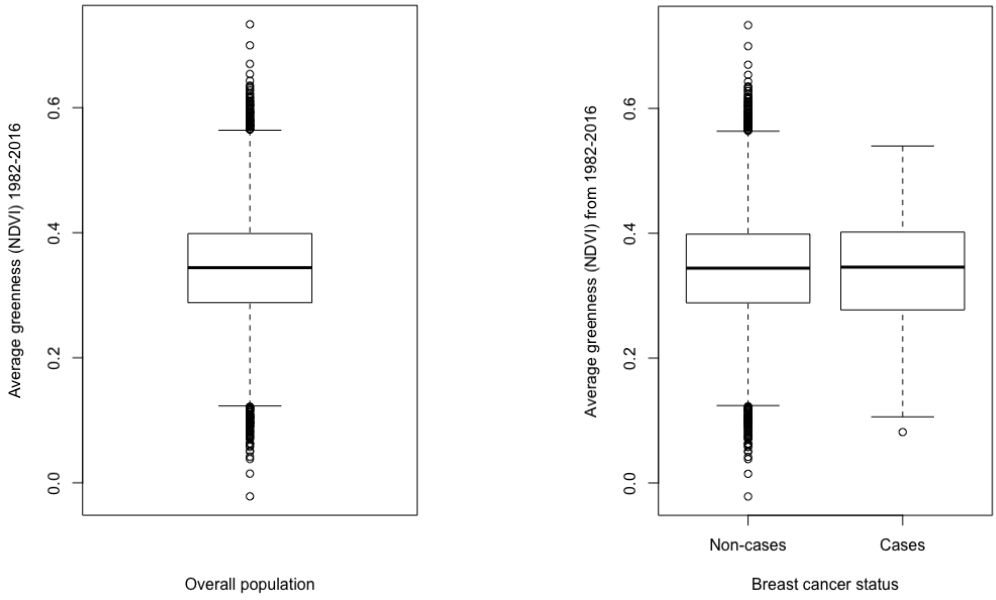

Figure 8: Average greenness (NDVI) for cases and non-cases between 1982 – 2016

4.3.1.4 Relationship between built environmental factors

A moderately strong positive Spearman correlation (Table 8) was found between baseline air pollution (NO_2) and baseline walkability z-score (r = 0.61, p = <0.01), a finding consistent with another study that correlated NO_2 and walkability in the same region.[125] The correlation was less strong for the average NO_2 exposure between the years of 1980 – 2012 and baseline walkability (r = 0.48, p = <0.01). Moderately weak correlations were found between baseline greenness (NDVI) and air pollution (r = -0.36, p = <0.01), and between average NDVI and average NO_2 concentration (r = -0.37, p = <0.01). Finally, the relationship between walkability and greenness also resulted in a moderately weak negative correlation between baseline greenness and baseline walkability (r = -0.32, p = <0.01) and between average greenness over the time period of 1982 – 2016 and baseline

walkability (r = -0.34, p = <0.01). People in less walkable areas tend to live towards the edge of a region with increased vegetative cover.

Table 8: Spearman correlations between built environment variables

	BL air pollution	Avg air pollution	BL Walkability	BL greenness	Avg greenness
BL air pollution	1	0.79 (0.01)	0.61 (<0.01)	-0.37 (<0.01)	-0.34 (0.01)
Avg air pollution	0.79 (0.01)	1	0.48 (<0.01)	-0.36 (<0.01)	-0.36 (<0.01)
BL Walkability	0.61 (<0.01)	0.48 (<0.01)	1	-0.32 (<0.01)	-0.34 (<0.01)
BL greenness	-0.37 (<0.01)	-0.36 (<0.01)	-0.32 (<0.01)	1	-0.37 (<0.01)
Avg greenness	-0.34 (0.01)	-0.36 (<0.01)	-0.34 (<0.01)	-0.37 (<0.01)	1

Abbreviations: Avg: Average; BL: Baseline
Note: Air pollution (NO_2) is measured in ppb, greenness is measured in NDVI and walkability is measured using a z-score. P-value is represented in brackets.

4.4 Multivariable analysis – Cox PH regression

4.4.1 Air pollution (NO_2)

The full model for baseline TRAP (NO_2, measured in ppb) included all 15 covariables of interest as discussed in Section 3.6.2. In the full model, the HR for a 10 ppb increase in NO_2 was of 1.49 (95% CI = 0.86, 2.60; p = 0.16). The final adjusted model was found using the change-in-effect model building process described in Section 3.6.2. A table presenting the results for the change-in-estimate modelling procedure is provided in the Appendix, Table A2. The final adjusted model included BMI and social deprivation. The HR from this final model for a 10 ppb increase in baseline NO_2 was 1.45 (95% CI = 0.90, 2.33, p = 0.12; Table 9). The concordance for this model was 0.59. There were a total of 43,027 person-years and 91 incident breast diagnoses included in this model and a total of 1545 observations excluded due to missing data (31 breast cancer cases lost to missing data).

Table 9: Baseline TRAP (NO_2) change-in-effect Cox PH model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Air pollution (NO_2) per 10 ppb increase*	1.45	0.90	2.33	0.12
BMI**	1.01	0.98	1.05	0.45
Social deprivation***	-	-	-	0.01
Q1 (32 cases, 10,713 pys)	1.00	-	-	-
Q2 (19 cases, 8,411 pys)	0.74	0.42	1.30	0.30
Q3 (11 cases, 7,290 pys)	0.48	0.24	0.95	0.04
Q4 (15 cases, 7,970 pys)	0.55	0.29	1.05	0.07
Q5 (14 cases, 8,233 pys)	0.49	0.25	0.94	0.03

Abbreviations: BMI: body mass index; CI: Confidence Interval; HR: Hazards ratio; NO_2: Nitrogen dioxide; p: p-value; pys: person-years Q: Quintile
* Adjusted for BMI and social deprivation
** Adjusted for NO_2 and social deprivation
*** Adjusted for NO_2 and BMI

The Schoenfeld's test for proportional hazards resulted in a p-value of 0.53 for NO_2 and a global p-value of 0.39. All other p-values for the Schoenfeld's test were also above 0.05, therefore the proportional hazard assumption was met (p-values for BMI = 0.52 and social deprivation = 0.22).

Breast cancer risk associated with the average longitudinal TRAP exposure (between the years of 1980-2012) was also determined. The full model had an HR estimate of 1.34 (95% CI = 0.85, 2.12; p = 0.20) for a 10 ppb increase in average NO_2. The change-in-effect process identified the same two covariates as the baseline pollution model as confounders: BMI and social deprivation (Table 10). A table for the results for the change-in-estimate process are provided in the Appendix, Table A3. The estimated HR for averaged air pollution was 1.41 per 10 ppb (95% CI = 0.95, 2.08; p 0.09). This HR estimate was similar to that of baseline air pollution. The concordance was 0.58 and there was a total of 42,936 total person-years and 91 incident breast cancer diagnoses included

and 1501 participants excluded due to missing data (31 breast cancer cases excluded). The proportional hazards assumption was met (Schoenfeld's test p-value = 0.70, 0.52, 0.22, 0.39 for air pollution, BMI, social deprivation and global, respectively).

Table 10: Averaged TRAP (NO_2) from 1980 – 2016 change-in-effect Cox PH model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Air pollution (NO_2) per 10 ppb increase*	1.41	0.95	2.08	0.09
BMI**	1.01	0.98	1.05	0.45
Social deprivation***	1.00	-	-	0.02
Q1 (32 cases, 10,689 pys)	1.00	-	-	-
Q2 (19 cases, 8,402 pys)	0.74	0.42	1.30	0.29
Q3 (11 cases, 7,268 pys)	0.48	0.24	0.95	0.04
Q4 (15 cases, 7,965 pys)	0.56	0.30	1.06	0.07
Q5 (14 cases, 8,211 pys)	0.51	0.27	0.96	0.04

Abbreviations: BMI: body mass index; CI: Confidence Interval; HR: Hazards ratio; NO_2: Nitrogen dioxide; p: p-value; pys: person-years Q: Quintile
* Adjusted for BMI and social deprivation
** Adjusted for NO_2 and social deprivation
*** Adjusted for NO_2 and BMI

4.4.2 Walkability

For walkability analyses, a quintile variable was used. Quintile 1 represents the least walkable areas, while quintile 5 represents the most walkable. The full model for walkability included all 15 covariates – the HR for quintiles 2 though 5 in relation the quintile 1 were 1.70, 2.49, 2.69 and 1.75, with a test for trend p-value of 0.09. Using the change-in-effect procedure, the final adjusted model included only social deprivation. A table for the results of the change-in-estimate process are provided the Appendix, Table A4. The p-value for the test for trend for walkability was 0.06. The adjusted HRs for quintiles 2 though 5, in relation to quintile 1, were 1.67, 2.53, 2.24 ad 1.83 (Table 11), signifying the least walkable area (quintile 1) had the lowest risk. This model included

49,666 total person-years, 112 incident breast cancer cases and excluded 653 participants due to missing data (10 breast cancer cases excluded).

Table 11: Categorical walkability change-in-effect Cox PH model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Walkability (Can-ALE)*	-	-	-	0.052
Q1 (13 cases, 9,746 pys)	1.00	-	-	-
Q2 (21 cases, 9,737 pys)	1.67	0.84	3.34	0.15
Q3 (31 cases, 9,805 pys)	2.53	1.32	4.84	0.01
Q4 (27 cases, 9,881 pys)	2.24	1.14	4.36	0.02
Q5 (20 cases, 10,497 pys)	1.83	0.85	3.94	0.12
Social deprivation**	-	-	-	0.08
Q1 (36 cases, 12,635 pys)	1.00	-	-	-
Q2 (25 cases, 9,930 pys)	0.86	0.52	1.43	0.56
Q3 (14 cases, 8,510 pys)	0.55	0.29	1.03	0.06
Q4 (17 cases, 9,260 pys)	0.59	0.32	1.09	0.09
Q5 (20 cases, 9,332 pys)	0.69	0.37	1.26	0.23

Abbreviations: BMI: body mass index; CI: Confidence Interval; HR: Hazards ratio; p: p-value; pys: person-years Q: Quintile
Note: Quintile 5 is the highest walkability
** Adjusted for social deprivation
** Adjusted for walkability

The proportionality assumption was tested using the Schoenfeld's test of proportional hazards. The p-value for walkability and social deprivation were 0.053 and 0.35 respectively, and the global p-value was 0.69, therefore the proportionality assumption was met. The model concordance was 0.61.

4.4.3 Greenness

Models for greenness used NDVI as a continuous variable as well as a categorical variable. In the full model, the HR for baseline greenness was 0.99, (95% CI = 0.71, 1.39; p = 0.95) for a 1-IQR

increase (IQR = 0.168). The change-in-effect procedure did not identify any variables as a confounder (Table 12). A table for the results of the change-in-estimate process are provided the Table A5 in the Appendix, the model did not include any other variables. The unadjusted change-in-effect model HR for a 1-IQR increase in baseline greenness was 0.96 (95% CI = 0.75, 1.23; p = 0.76). The concordance was 0.48. There was a total of 51,292 person-years and 113 incident breast cancer diagnoses included in this model – 418 participants were excluded due to missing data (nine of which were participants with breast cancer). The PH assumption for the adjusted model was met, greenness had a p-value of 0.14 (the global p-value was the same because no other covariates were included in the adjusted model).

Table 12: Greenness (NDVI) change-in-effect Cox PH model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Baseline greenness (NDVI)*	0.96	0.75	1.23	0.76

Abbreviations: CI: Confidence Interval; HR: Hazards ratio; NDVI: Normalized Difference Vegetation Index p: p-value; pys: person-years
*Unadjusted

The baseline greenness model was also presented using a categorical tertile variable for greenness (Table 13). Tertile 1 were those with low NDVI exposure (areas with less surrounding greenness), whereas tertile 2 and 3 had medium and high had exposure, respectively. The categorical variable for greenness had an overall p-value of 0.42. The medium and high tertiles had HRs of 0.76 and 1.01 in relation to the tertile 1 (test for trend p-value = 0.98).

Table 13: Categorical baseline greenness (NDVI) change-in-effect Cox PH model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Baseline greenness (NDVI)*	-	-	-	0.98
Low (41 cases, 17,124 pys)	1.00	-	-	-
Medium (31 cases, 17,098 pys)	0.76	0.48	1.21	0.25
High (41 cases, 17,070 pys)	1.01	0.65	1.55	0.98

Abbreviations: CI: Confidence Interval; HR: Hazards ratio; NDVI: Normalized Difference Vegetation Index p: p-value; pys: person-years
*Unadjusted

A model for average longitudinal greenness exposure between the years of 1982 and 2016 (Table 14). In the full model, the HR for average greenness exposure was 0.69 (95% CI = 0.43, 1.09; p = 0.11) for a 1-IQR increase (IQR = 0.111). The adjusted model used only social deprivation as a covariate. A table for the results of the change-in-estimate process are provided Appendix, Table A6. The adjusted HR for average greenness exposure was 0.80 for a 1-IQR increase (95% CI = 0.63, 1.02; p = 0.07). The model concordance was 0.57. There was a total of 50,0031 person-years and 112 incident breast cancers included in this model – 580 participants were excluded due to missing data (10 of which were participants with incident breast cancer). The PH assumption for the adjusted model was met – greenness had a p-value of 0.13, social deprivation had p = 0.38 and a global p-value of 0.42.

Table 14: Average greenness (NDVI) between 1982-2016 change-in-effect Cox PH model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Averaged greenness (NDVI)*	0.80	0.63	1.02	0.07
Social deprivation**	-	-	-	0.04
Q1 (36 cases, 12,538 pys)	1.00	-	-	-
Q2 (25 cases, 9,857 pys)	0.87	0.52	1.45	0.59
Q3 (14 cases, 8,553 pys)	0.55	0.29	1.02	0.06
Q4 (17 cases, 9,296 pys)	0.57	0.32	1.03	0.06
Q5 (20 cases, 9,308 pys)	0.64	0.36	1.14	0.13

Abbreviations: CI: Confidence Interval; HR: Hazards ratio; NDVI: Normalized Difference Vegetation Index p: p-value; pys: person-years
*Adjusted for social deprivation
**Adjusted for NDVI

This longitudinal greenness model was also presented using a categorical tertile variable for greenness (Table 15). The categorical variable for greenness had a p-value of 0.22. The medium and high tertiles had HRs of 0.69 and 0.71, in relation to the tertile 1 (test for trend p = 0.15).

Table 15: Categorical greenness (NDVI) between 1982-2016 change-in-effect Cox model

Variable	HR	95% CI (lower bound)	95% CI (upper bound)	p
Averaged greenness (NDVI)*	-	-	-	0.15
Low (40 cases, 16,620 pys)	1.00	-	-	-
Medium (31 cases, 16,156 pys)	0.69	0.43	1.10	0.12
High (41 cases, 116,777 pys)	0.71	0.45	1.13	0.15
Social deprivation**	-	-	-	0.05
Q1 (36 cases, 12,538 pys)	1.00	-	-	-
Q2 (25 cases, 9,857 pys)	0.87	0.52	1.46	0.60
Q3 (14 cases, 8,553 pys)	0.55	0.30	1.02	0.06
Q4 (17 cases, 9,296 pys)	0.59	0.33	1.05	0.07
Q5 (20 cases, 9,308 pys)	0.66	0.37	1.17	0.15

Abbreviations: CI: Confidence Interval; HR: Hazards ratio; NDVI: Normalized Difference Vegetation Index p: p-value; pys: person-years
*Adjusted for social deprivation
**Adjusted for NDVI

Chapter 5: Discussion and conclusion

5.1 Findings

5.1.1 Overview and interpretation of findings

Our study assessed the impact of TRAP, walkability, and greenness on breast cancer risk in post-menopausal women in the Lower Mainland of BC. Our study was comprised of 7,330 participants, with 122 incident breast cancer diagnoses. Non-significant HRs were found for all three environmental measures, for both baseline and average longitudinal exposures. Although not statistically significant, the TRAP models had similar magnitudes of risk compared to other studies in the literature. There is very little research to date measuring the direct association of walkability and greenness and breast cancer risk. More research is needed to understand if these non-significant results are underpowered or due to confounding and/or exposure misclassification.

5.1.2 Air pollution

This is the first study assessing the impact of TRAP on post-menopausal breast cancer risk in the Lower Mainland of BC. The adjusted HR for baseline TRAP (NO_2) was 1.45 (95% CI = 0.90, 2.33, p = 0.12) for a 10 ppb increase in NO_2. Similarly, the adjusted HR for average longitudinal NO_2 exposure was 1.41 (95% CI = 0.95, 2.08, p = 0.09) for a 10 ppb increase. This suggests that in the BCGP and the Lower Mainland, a baseline air pollution measure may be a good marker for longitudinal exposure.

To date, there has been suggestive evidence of the impact of TRAP as a risk factor for breast cancer risk in the literature.[66] While several Canadian and international studies which have found

significant results, others have reported non-significant findings. Although the findings of our study were also non-significant, the magnitude of risk was in the same range as most other studies reporting increased risk of breast cancer associated with TRAP. The majority of studies to date investigating TRAP and breast cancer risk were done using a case-control design. This study was one of the few which used a longitudinal cohort design with Cox regression modeling.

Significant results of similar magnitude to our study were identified in two Canadian studies. A study by Hystad et al.,[16] measured the association between NO_2 and breast cancer in a case-control study of urban centres across eight Canadian provinces, and included approximately 1,500 cases and 1,500 controls. Hystad investigated pre- and post-menopausal women. The fully adjusted model included age and province, BMI, alcohol, smoking, PA, routine mammography, second-hand smoke and various women's health variables. The adjusted odds ratio (OR) was 1.07 (95% CI = 0.86, 1.32). The Hystad study also conducted stratified analyses by province by randomly sampling breast cancer cases from each province to match a pre-determined sample quota. The adjusted OR for BC was 1.54 per 10 ppb (95% CI = 0.95, 2.51). The magnitude of this effect was similar to our study; however, the CI was much larger, and the authors noted that the inflated BC results may have been due to BC having the largest oversampling of breast cancer cases. Hystad and colleagues also noted positive associations for pre-menopausal women, with an OR of 1.28 (95% CI = 0.92, 1.79) per 10 ppb. Another smaller case-control study, set in Montréal, included 383 cases and 416 controls.[11] In the study, Crouse et al. found a significant OR of 1.31 (95% CI = 1.00, 1.71) per 5 ppb increase (or an OR of 1.72 per 10 ppb, 95% CI = 1.00, 2.92), after adjusting for similar pre-selected confounders as the Hystad study. Both of these Canadian studies used case-

control designs, which can have limitations such as recall, selection and screening biases, as well as a lack of longitudinal exposure,[11] something our cohort design was able to account for.

A large Canadian cohort study by Goldberg et al. analysed 89,247 women in a national study.[4] The cohort was composed of women between the ages of 40 and 59, with menopausal status being determined by two separate age cut-offs of 50 and 52 – approximately 39% of the study population was considered to be post-menopausal. The cohort included 5,851 incident breast cancer cases, 47% of which were in post-menopausal women. Similar to our study, Goldberg used Cox proportional hazards models to estimate time-to-event risk. The authors assessed five pre-determined models which accounted for various confounders, and for two different post-menopausal age cut-offs: 50 and 52. For post-menopausal cohorts, little evidence of association was found. Using an age cut-off of 52 years, the post-menopausal fully adjusted models had a rate 1.01 (95% CI = 0.96, 1.06) per 1-IQR of 9.7 ppb (rounded to two decimal points, this result does not change per 10 pp increase), with very similar results for the 50 year cut-off. In contrast, in pre-menopausal cohorts, based on age alone, stronger magnitudes of association were found, with fully adjusted RRs of 1.17 (95% CI = 1.00, 1.38) and 1.13 (95% CI = 0.94, 1.37) for age cut-offs of 52 and 50, respectively. Our study appears to benefit from a more accurate measure of post-menopausal status. Although these Canadian results were not specific to the BC Lower Mainland, certain population characteristics would be similar due to the Canadian context of the study.

There have also been studies on TRAP and breast cancer incidence conducted outside of a Canadian setting. Andersen et al. conducted a large European based longitudinal cohort study measuring the effect long-term ambient air pollution on incidence post-menopausal breast

cancer.[59] The authors measured multiple traffic-related pollutants, but found non-significant results for NO_2 (HR=1.02 per 10 µg/m^3, 95% CI = 0.98, 1.07). Note that 1 ppb is equal to 1.25 µg/m^3 at 1 under standard conditions, 1 atmosphere and a temperature of 25° Celsius.[126] The Andersen study also found non-significant results for other pollutants, including for $PM_{2.5.}$, PM_{10} and PM_{coarse}, but, did however find a significant result for NO_x with an HR of 1.04 per 10 µg/m^3, (95% CI = 1.00, 1.08, p = 0.04).

The statistically non-significant results in our study may be attributed to reduced power due to the relatively small sample size, or potentially the lower overall ambient air pollution (NO_2 and PM) and lower variation in air pollution in Vancouver and the Lower Mainland than found elsewhere, although the effect size was similar to those reported elsewhere. Most of the Canadian breast cancer research in relation to air pollution has been conducted in Montréal. Although ambient traffic-related pollution levels are similar in the two cities, they are not directly comparable. Both Montréal and Vancouver have similar NO_2 concentrations (average: 10.9 and 11.1 respectively, over the years 2009 to 2014) which are far below the WHO guidelines (21.2 ppb).[127] As discussed, TRAP consists of a mixture of different gasses, particulate matter and other volatile organic compounds. Nitrogen dioxide is not yet classified a carcinogen; however, it is often used as a marker for other cancer-causing agents, including particulate matter.

Although Vancouver and Montréal have similar NO_2 levels, particulate matter concentration in Montréal are more than double those in Vancouver (average: 10.2 and 4.9 mcg/m^2 respectively, over the years 2009 to 2014), and surpasses the WHO guideline for PM (10 mcg/m^2). Due to these smaller concentrations of air pollution in Vancouver and the Lower Mainland, the association

between air pollution and breast cancer risk may be harder to detect. Similarly, Vancouver also has low levels of NO_2 and PM compared to larger international cities like Boston, London and Hong Kong, which double or even triple WHO guidelines. Further research some into the effect of TRAP in areas exceeding these guidelines is key to fully understanding the effect it has on breast cancer risk.

The Andersen study, as well as some of the other studies previously mentioned, noted a key limitation in that it lacked early lifetime exposure to air pollution. Crouse et al. noted, participants are not likely to live in the same house over a lifetime which is why a longitudinal measure of exposure is necessary.[11] Because of this, measures of ambient air pollution to study participants can be difficult. Due to the linkage of the CANUE environmental consortium with the BCGP cohort, our study was able to capture an average NO_2 over the past 32 years accounting for changes in residence throughout this time period. This longitudinal pollution exposure mapped to past residences is fairly unique to this study and helps fill a gap in the literature.

Some of the current literature have shown results suggesting an association between TRAP and breast cancer incidence, however, results across studies have not all been conclusive. While our study provides a unique view of this association in the Lower Mainland of BC, no significant association was found. More research is needed to be able to determine if TRAP is a significant contributor to breast cancer risk in post-menopausal women.

5.1.3 Walkability

This is the first study to our knowledge to be conducted measuring the direct effect of urban walkability on breast cancer risk. The walkability model had HRs adjusted for social deprivation, ranging from 1.67 to 2.53 for quintile 2 though 5 (quintile 5 being most walkable), with the highest being quintile 3. The test for trend of an overall difference across categories gave a p-value of 0.06. The adjusted HRs for quintiles 2 through 5, in relation to quintile 1, were all greater than 1, indicating that quintile 1 (the least walkable) had the lowest breast cancer risk. The greatest adjusted HR, in relation to quintile 1, was quintile 3 with a HR of 2.53 (95% CI = 1.14, 4.36).

It is possible the lack of an observed significant effect is a function of type II error where the null hypothesis is accepted rather than dismissed. Type II error may be a function of how walkability measures were assessed from Can-ALE. The Can-ALE data used in this study is based on land area and is "2-dimensional" or flat rather than a "3-dimensional" floor space approach built from property assessment parcel level data (Frank et al 2021 – in press). Developing walkability measures over large geographies such as all of Canada or the US typically requires using land area rather than floor space data. It is also interesting to note that increasing walkability was associated with increasing breast risk. This result appears counter-intuitive and is contrary to most literature on walkability and chronic disease.[20,128,129] This may be due to residual confounding, in that the more walkable areas may be the most affluent, the possibility that there is not enough variability in the dataset . Further research is required to understand this association.

The scoping review in Chapter 2 was unable to uncover any studies investigating this association. One study did, however, investigate the effect of walkability on breast cancer mortality. This study

did find that increased walkability was associated with lower risk of breast cancer mortality. Higher rates of breast cancer mortality were found in more car dependent areas with lower walkability.[19] Although their research was not studying walkability in relation to breast cancer risk, breast cancer mortality does offer some insight into a possible association between walkability and breast cancer. Unfortunately, the entirety of this publication was not in English and only the abstract was able to be reviewed.

Unlike air pollution and greenness, there is no direct measure for walkability and therefore a variety of indices have been derived using similar variables to construct the index. The Can-ALE index, used in our study, is one of these indices, however, other notable indices include Walk score, the Pedestrian Index of the Environment (PIE), the Vancouver Walkability Index (WI), the Neighborhood Destination Accessibility Index (NDAI), and the Pedestrian Potential Index (PPI).[130] Unfortunately, the Can-ALE index was only implemented in 2006 and therefore a longitudinal walkability measure study was not available. The Can-ALE walkability scores were measured differently at two timepoints – 2006 and 2016 – and are not comparable. Therefore, only the 2006 measure was used and was extrapolated to the residence at entry. Since most participants were enrolled into the BCGP around this timepoint, it is expected that this Can-ALE still provides a reasonable representation of their residence at enrolment, however, it cannot be representational for the lifetime exposure of participants most of whom have lived in a variety of locations with varying levels of walkability. Walkability in a given location is also subject to change over time as communities add new development, land uses change, and improvements are made to street design. These changes to walkability have been shown to affect vehicle use and carbon emission, physical activity and walking volume in communities.[125,131]

Another aspect of walkability is the amount individuals interreact with their local environment and walk within their neighbourhood. Similar points could be made for green space and air pollution – whether certain individuals interact enough or spend sufficient time near their residence to truly be exposed to their surroundings. An Australian study found a strong correlation between walkability and amount weekly walk by individuals, after controlling for SES, ages and gender.[90] Our study did not investigate whether this was the case in the BCGP, however a study by Colley et al. for Statistics Canada did investigate this using the CAN-ALE.[132] The Canada-wide study used the Canadian Health Measure Survey, an ongoing cross-sectional Statistic Canada study from a representative national sample. The authors used linear regression models, adjusting for age, sex, household income and measured PA using questionnaires and as accelerometers found a positive linear trend between the Can-ALE index and physical activity. Although these results cannot necessarily be extrapolated to the BCGP specifically, they do provide a consensus that there is a positive relationship between the walkability of one's neighbourhood and the amount they are physically active. Further investigation should be done within the BCGP.

Although there have been no previously published studies on breast cancer risk in relation to walkability, there is a plethora of studies investigating walkability and obesity. These studies have provided evidence that increased walkability is associated with a healthier BMI.[84,91] As discussed in the scoping review, both increased BMI and obesity are known to be significant risk factors for breast cancer.[86–89] Although there is there is currently no significant evidence of a direct association with breast cancer risk and walkability, the indirect link through BMI and obesity may play a role in breast cancer risk.

The relationship between walkability and air pollution may also be an important factor which should be investigated in future studies. Dense metropolitan areas tend to be the most walkable, as well as the most polluted. Our study noted a positive correlation between increased air pollution and increase walkability (BL cor = 0.57, p = <0.01, longitudinal cor = 0.43, p = <0.01). A similar finding was observed in Vancouver-based study conducted by Marshall et al.[125] Their study investigated how the built environment influences health through physical activity and air pollution. Marshall and colleagues, using a different index of walkability, also found evidence that many areas with high walkability had the highest concentrations of TRAP. They also noted that neighbourhoods with high walkability and low pollution were rare – they were mainly located near, but not within, the city centre and primarily in high SES neighbourhoods.

Although statistically significant findings were not found, this study helps direct attention to an understudied area. Future studies investigating the effects of walkability on breast cancer are warranted. It is also important to understand the relationship between walkability and other aspects of the built environment and their corresponding effect on cancer.

5.1.4 Greenness

The adjusted HR for baseline greenness was 0.96 (95% CI = 0.75, 1.23, p = 0.76) for a 1-IQR increase (IQR = 0.168) in NDVI. Similarly, the adjusted model for longitudinal greenness exposure HR of 0.80 (95% CI = 0.63, 1.02, p = 0.07) for a 1-IQR increase (IQR = 0.111), implying a reduction of breast cancer risk associated with increased greenness, albeit statistically non-

significant. Although not significant, these findings may imply increased greenness offers a protective effect for breast cancer.

As with walkability, there was been very little published research with respect to greenness and breast cancer risk. A Spanish case-control study by O'Callaghan-Gordo et al. investigated the association between residential proximity to green space and breast cancer risk, with over 1,000 cases and controls, respectively.[18] Their study used NDVI to measure exposure to green space at 100m, 300m and 500m. The authors used logistic mixed-effects regression, with random effects for hospitals, and adjusted for age, education, SES and number of children. It was found that the presence of urban green spaces – residing within 300m of urban green space (e.g., parks, zoos, gardens, etc.) – was significantly associated with reduced risk of breast cancer (OR = 0.65; 95% CI = 0.49, 0.86), after adjusting for confounders. Interestingly, O'Callaghan-Gordo et al. found the opposite effect in agricultural areas – the presence of green space was associated with an increased risk (OR = 1.33, 95% CI = 1.07, 1.65). The authors also concluded increased surrounding greenness (NDVI) within 300m was associated with increased breast cancer risk (OR = 1.20 per 1-IQR; 95% CI = 1.07, 1.34). This finding is opposite to what was found in our study; however, the authors do indicate that this increased risk is may have been driven by the positive association agricultural areas, as these areas tended to have higher NDVIs. This effect of agricultural areas would likely be less pronounced in our study as it was restricted to urban areas. O'Callaghan-Gordo et al. did restrict the study in a sub-analysis of participants who lived in the residence at least 10 years prior enrolment and found consistent findings. They also found consistent findings when restricting to urban areas of greater than 100,000 residents.

Further, the Spanish study investigated an important aspect of the relationship between green space and breast cancer risk – the mediation through physical activity (PA) and air pollution – which was not thoroughly investigated in our study. They hypothesized that any association would be mediated by either PA or pollution levels, however, their results did not support this mediation effect. The green space model in our study used PA in the change-in-effect model building process, but it was not found to be a significant confounder. O'Callaghan-Gordo and colleagues found similar PA levels regardless of presence of green space. Consistent findings have been identified in two studies investigating this topic.[133,134] Both authors found that PA does not explain the association between green space and health. It is noted, however, that these findings may be specific to the region studied and may reflect aspects of social and cultural patterns of the population studied or specific characteristics about the green space itself. The Spanish study also discussed the relationship between that urban green space and air pollution. They found that people living near green areas were exposed to higher PM levels as well as similar NO_2 levels to those living further away from green areas. An opposite association was identified in our study, participants living in areas with high NDVI were exposed to less air pollution, however, only a moderately weak correlation was observed (BL cor = -0.36; p = <0.01, and longitudinal cor = -0.37; p = <0.01).

Similar to our study, the O'Callaghan-Gordo study benefitted from accurate measures of green space and breast cancer diagnoses. However, the authors also noted difference in SES between cases and controls – indicating there may have been selection bias. The BCGP and CANUE linkage in this study was able to provide measures of community level SES and deprivation. The O'Callaghan-Gordo study also benefitted from multiple distances to green spaces. Further

investigation of the BCGP using different measures of green space may be important to consider in future research. A limitation with baseline green space annual measurements is that they can vary from year to year, depending on the amount of rainfall. Because of this, assigning quintiles baseline may result in misclassification when participants joined the study in different years. An advantage of our study was in its cohort design which was able to assign longitudinal exposure. As with walkability, the scientific community would benefit from further investigation into this area.

5.2 Strengths and limitations

5.2.1 Limitations

One limitation which arises from the of environmental exposure data used in this study is that the exposure experienced at the home location only captures part of an individual's exposure. For example, workers typically spend the majority of their weekdays elsewhere where environmental factors are quite different. Second, for both air pollution and green space, the CANUE dataset allowed a measure of longitudinal NO_2 concentrations and NDVI, however, for walkability a similar longitudinal measure was not available. Walkability scores were extrapolated to the residence at study enrolment. Baseline measurements may not be a good representation of lifetime exposure of walkability, which would be a much better indicator of breast cancer risk. People generally move a number of times over their life course. The average person in the US moves 11.7 times in their lifetime and Statistics Canada has indicted that about half of Canadians have moved within the past five years or plan to move in the next five.[135,136] All measures of the built environment would greatly benefit from more precise spatial geography, such as capturing work as well as home locations, or using floor space data when possible to enable the 3-dimensional

nature of the built environment to be captured.[72,137,138] Finally, the definition of post-menopausal status may present some limitations. Menopausal status was asked in the questionnaire at baseline, but unlike cancer diagnosis, there was no follow-up for menopausal status. Age alone is not a definitive indicator of menopause, therefore there may be some misclassification present, however it is likely to be non-differential.

Similar to any study of the built environment, understanding the extent to which an individual interacts directly with their environment can be challenging. A participant may live in an area with low pollution exposure but spend most of their day at work in area with high exposure. Similarly, a participant may live in a highly walkable neighbourhood, but perhaps never chooses to walk for exercise or as a mode of transport. However, this exposure misclassification would also likely be non-differential and therefore attenuate the results towards the null hypothesis. Being able to account for these confounders would make the study design much stronger. Finally, although the BCGP had a reasonable number of incident breast cancer, the relatively small sample size limits the statistical power.

5.2.2 Strengths

This study benefited from several key methodological strengths. Importantly, this study was able to take advantage of a large prospective cohort along with linked environmental exposure information and incident cancer diagnoses. The two datasets have been linked using individual residential postal code data at enrolment and residential history. This linkage allowed longitudinal environmental exposures before cancer diagnosis to be analysed for green space and air pollution exposure. This is a particular advantage, as longitudinal information has not always been available

in previous air pollution breast cancer studies, and many studies have only used baseline measurements.

Another key strength of this analysis is in the study design itself. The longitudinal cohort design allowed cancer incidence to be measured. Having breast diagnoses linked from the provincial cancer registry is a major strength due to the to the completeness and accuracy of the BC Cancer registry. Finally, the CANUE environmental dataset provided consistent and reliable measures of air pollution, linked to participant, as well as metrics for neighbourhood social and material deprivation. As noted in the scoping review, deprivation and marginalization have been found to be key confounders to for environmental risks on breast cancer. Using the change-in-estimate model building approach, both social and material deprivation were found to be important confounders in almost all models. Measures of deprivation are often not easily attainable, and therefore provide a great advantage to this study.

5.3 Study implications

Breast cancer presents a serious global burden, and in many instances can be prevented by modifying environmental and lifestyle factors.[1–4,6] Recent studies have demonstrated how characteristics associated with the built environment can impact many aspects of health, which reinforces the importance of research in breast cancer prevention in relation to urban planning and pollution levels.[139] Although no significant results were found, statistical significance was approached in all three built environment characteristics. Our study can help inform the scientific community that further built environment research is needed in relation to these modifiable potential breast cancer risk factors. Given that other studies have linked the same data with 3-

dimensional parcel level walkability and green space and have found significant relationships with physical activity and obesity (known risk factors for breast cancer), it is therefore possible that breast cancer may also be associated with these same environmental exposures.

5.3.1 Public health implications

To date, the understanding of the association between the built environment and breast cancer risk is still its infancy. Most of the research has been done in relation to TRAP, however, this evidence is still only suggestive, and more research needs to be done to understand this relationship conclusively. That being said, there are large health benefits in having a sustainable and healthier city.[140,141] There have been numerous studies investigating air pollution, walkability and green space in relation to other cancers, PA and obesity, mental health, and other chronic diseases.[20,99,128,129,142]

These three characteristics of the built environment have both direct effects on health, as well as indirect effects, as indicators that influence health behaviours. TRAP is a known carcinogen and it has been well established to cause certain types of cancers as well as other chronic respiratory diseases.[99,143] TRAP can also be related to neighbourhood planning, public transportation, and traffic density, and transportation alternatives, such as walkability. Walkability allows for the easy adoption of healthy behaviours for recreation or commuting, through walking, running or other means of physical activity. As mentioned, there are many published studies that document the association between increased physical activity, decreased BMI and health benefits.[20] Likewise, access green space and greenness has been shown to be protective against mental health outcomes as well as cardiovascular disease.[144] There are theories which posit a direct affect, including

decreased stress.[145] Access to green spaces also provide opportunity for social interaction and opportunity for physical activity.[144]

As a result, when studying the urban environment, it important to understand the relationship between TRAP, walkability and green space within a city, as their existence is not in isolation. Although not the objective of our study, significant correlations were found between all three aspects of the built environment. A study by Frank et al. investigated the relationship between obesity, physical activity and time spent in cars.[91] The study found that each additional hour spent in a car was associated with a 6% increase in likelihood of obesity, whereas each additional kilometre walked per day was associated with a 4.8% reduction in obesity. In another study by Frank, investigators aimed to understand the interaction between neighbourhood walkability and air pollution on health.[146] This Seattle-based study found that a 5% increase in walkability to be associated with 32.1% increase in physically active transport (walking and biking), per capita, and a 0.23-point reduction in BMI. Likewise, Frank found this same increase in walkability to be associated with 6.5% fewer vehicle miles travelled and subsequently, 5.6 fewer grams of NO_x emitted. This finding creates a solid connection between walkability and TRAP and its effect on BMI – a significant risk factor for breast cancer, specifically in post-menopausal women.[43]

5.3.2 Public policy

Public policies can operate on many levels. At macro planning levels, urban spaces can be designed to help minimize exposure to traffic. This can result in decreased concentrations of motor vehicles in crowded urban areas and community spaces, as well as increased public transit

alternatives to gasoline powered vehicles. Other macro strategies include congestion pricing and regulatory approaches to eliminate or reduce all forms of carbon based transport in city centres is being explored globally.[147] A study by Coughlin and King indicate that the location of cancer diagnostic and treatment centres can also be a barrier to accessing health services.[148] The authors found that public transportation routes can play a role in whether women have access appropriate health services. Coughlin and Smith observed that public policy at the community level can promote healthy lifestyles through establishment of bike lanes, green spaces and greenways.[17] A study by Ray et al. reviewed how cancer prevention is influenced by the built environment.[12] The authors indicated how factors of the built environment like transportation, urban design, land use and green spaces affect breast cancer though metrics like air quality, obesity, physical activity and screening. Although the association between the built environment in our study were not significant, there is plenty of evidence supporting the health benefits of a healthy city. Successful implementation of public policies to increase walkability and green space may either directly or indirectly reduce the burden of breast cancer.

5.4 Conclusion

Features of the built environment (including TRAP, greenness and walkability) represent an important set of modifiable characteristics that have been shown to influence many aspects of chronic disease and health status. TRAP has many known adverse health effects, including lung cancer and other respiratory diseases, however, its effect on breast cancer is still only suggestive in nature. While our study did not have statistically significant findings, the findings were of similar direction and magnitude to other results in the literature. It is important to note that the effect of air pollution on breast cancer risk was of borderline statistical significance, despite the

relatively low levels of urban air pollution in the Lower Mainland of BC compared to other urban centres. This study is one of the first to investigate the association between green space, walkability and the breast cancer risk in post-menopausal women. Further investigation into the effect is warranted to fully understand the effect of these factors on breast cancer risk. Understanding how the built environment affects breast cancer will support the development of appropriate policies to mitigate the risk.

5.5 Future recommendations

Further research is required in all three studied aspects of the built environment. TRAP has been studied in-depth; however, the field would greatly benefit from more research with longitudinal exposure, especially in areas with higher pollution levels. Breast cancer is a disease which develops over a long period of time and therefore lifetime exposure is necessary to better understand the effect TRAP has on breast cancer risk. Research on the other characteristics of the built environment in relation to breast cancer risk, walkability and green space, is still in its infancy. Further research is required to understand if there is a true association between pollution and these aspects of the built environment.

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Appendices

Appendix A: Supplementary tables

Table A1: 3-digit postal code FSA

Name	Description/ City Name	Code	Region	Province	Country
Abbotsford East	Port Coquitlam	V3G	Lower Mainland	BC	Canada
Abbotsford Southeast	Abbotsford	V2S	Lower Mainland	BC	Canada
Abbotsford Southwest	Abbotsford	V2T	Lower Mainland	BC	Canada
Abbotsford West	Abbotsford	V4X	Lower Mainland	BC	Canada
Burnaby (Burnaby Heights / Willingdon Heights / West Central Valley)	Burnaby	V5C	Lower Mainland	BC	Canada
Burnaby (Cascade-Schou / Douglas-Gilpin)	Burnaby	V5G	Lower Mainland	BC	Canada
Burnaby (East Big Bend / Stride Avenue / Edmonds / Cariboo-Armstrong)	Burnaby	V3N	Lower Mainland	BC	Canada
Burnaby (Government Road / Lake City / SFU / Burnaby Mountain)	Burnaby	V5A	Lower Mainland	BC	Canada
Burnaby (Lakeview-Mayfield / Richmond Park / Kingsway-Beresford)	Burnaby	V5E	Lower Mainland	BC	Canada
Burnaby (Maywood / Marlborough / Oakalla / Windsor)	Burnaby	V5H	Lower Mainland	BC	Canada
Burnaby (Parkcrest-Aubrey / Ardingley-Sprott)	Burnaby	V5B	Lower Mainland	BC	Canada
Burnaby (Suncrest / Sussex-Nelson / Clinton-Glenwood / West Big Bend)	Burnaby	V5J	Lower Mainland	BC	Canada
Chilliwack Central	Chilliwack	V2P	Lower Mainland	BC	Canada
Chilliwack East	Chilliwack	V4Z	Lower Mainland	BC	Canada
Chilliwack West	Chilliwack	V2R	Lower Mainland	BC	Canada
Coquitlam North	Coquitlam	V3J	Lower Mainland	BC	Canada
Coquitlam South	Coquitlam	V3K	Lower Mainland	BC	Canada
Delta Central	Delta	V4K	Lower Mainland	BC	Canada
Delta East	Delta	V4E	Lower Mainland	BC	Canada
Delta East Central	Delta	V4G	Lower Mainland	BC	Canada
Delta Northeast	Delta	V4C	Lower Mainland	BC	Canada
Delta Southeast	Delta	V4L	Lower Mainland	BC	Canada
Delta Southwest	Delta	V4M	Lower Mainland	BC	Canada
Harrison Lake Region (Agassiz)	NA	V0M	Lower Mainland	BC	Canada

Langley City	Langley	V3A	Lower Mainland	BC	Canada
Langley Township East	Langley Township	V4W	Lower Mainland	BC	Canada
Langley Township North	Chilliwack	V1M	Lower Mainland	BC	Canada
Langley Township Northwest	Langley Township	V2Y	Lower Mainland	BC	Canada
Langley Township Southwest	Langley Township	V2Z	Lower Mainland	BC	Canada
Maple Ridge East	Maple Ridge	V2W	Lower Mainland	BC	Canada
Maple Ridge Northwest	Maple Ridge	V4R	Lower Mainland	BC	Canada
Maple Ridge West	Maple Ridge	V2X	Lower Mainland	BC	Canada
Mission East	Maple Ridge	V2V	Lower Mainland	BC	Canada
Mission West	Mission	V4S	Lower Mainland	BC	Canada
New Westminster Northeast	New Westminster	V3L	Lower Mainland	BC	Canada
New Westminster Southwest (Includes Annacis Island)	New Westminster	V3M	Lower Mainland	BC	Canada
North Island, Sunshine Coast, and Southern Gulf Islands (Whistler)	NA	V0N	Lower Mainland	BC	Canada
North Vancouver East Central	Vancouver	V7J	Lower Mainland	BC	Canada
North Vancouver Inner East	Vancouver	V7H	Lower Mainland	BC	Canada
North Vancouver North Central	Vancouver	V7K	Lower Mainland	BC	Canada
North Vancouver Northwest	Vancouver	V7R	Lower Mainland	BC	Canada
North Vancouver Northwest Central	Vancouver	V7N	Lower Mainland	BC	Canada
North Vancouver Outer East	Vancouver	V7G	Lower Mainland	BC	Canada
North Vancouver South Central	Vancouver	V7L	Lower Mainland	BC	Canada
North Vancouver Southwest	Vancouver	V7P	Lower Mainland	BC	Canada
North Vancouver Southwest Central	Vancouver	V7M	Lower Mainland	BC	Canada
Pitt Meadows	Pitt Meadows	V3Y	Lower Mainland	BC	Canada
Port Coquitlam Central	Port Coquitlam	V3B	Lower Mainland	BC	Canada
Port Coquitlam North	Port Coquitlam	V3E	Lower Mainland	BC	Canada
Port Coquitlam South	Port Coquitlam	V3C	Lower Mainland	BC	Canada
Port Moody	Port Moody	V3H	Lower Mainland	BC	Canada
Richmond (Sea Island / YVR)	Richmond	V7B	Lower Mainland	BC	Canada
Richmond Central	Richmond	V6Y	Lower Mainland	BC	Canada
Richmond North	Richmond	V6X	Lower Mainland	BC	Canada
Richmond Northeast	Richmond	V6V	Lower Mainland	BC	Canada
Richmond South	Richmond	V7A	Lower Mainland	BC	Canada
Richmond Southeast	Richmond	V6W	Lower Mainland	BC	Canada
Richmond Southwest	Richmond	V7E	Lower Mainland	BC	Canada
Richmond West	Richmond	V7C	Lower Mainland	BC	Canada
Similkameen (Hope)	Langley Township	V0X	Lower Mainland	BC	Canada

Squamish	Squamish	V8B	Lower Mainland	BC	Canada
Surrey	Surrey	V3Z	Lower Mainland	BC	Canada
Surrey East	Surrey	V3S	Lower Mainland	BC	Canada
Surrey Inner Northwest	Surrey	V3T	Lower Mainland	BC	Canada
Surrey Lower West	Surrey	V3X	Lower Mainland	BC	Canada
Surrey North	Surrey	V3R	Lower Mainland	BC	Canada
Surrey Northeast	Surrey	V4N	Lower Mainland	BC	Canada
Surrey Outer Northwest	Surrey	V3V	Lower Mainland	BC	Canada
Surrey South	Surrey	V4P	Lower Mainland	BC	Canada
Surrey Southwest	Surrey	V4A	Lower Mainland	BC	Canada
Surrey Upper West	Surrey	V3W	Lower Mainland	BC	Canada
Vancouver (Bentall Centre)	Vancouver	V7X	Lower Mainland	BC	Canada
Vancouver (Central Kitsilano)	Vancouver	V6K	Lower Mainland	BC	Canada
Vancouver (Chaldecutt / South University Endowment Lands)	Vancouver	V6S	Lower Mainland	BC	Canada
Vancouver (Dunbar-Southlands / Musqueam)	Vancouver	V6N	Lower Mainland	BC	Canada
Vancouver (East Fairview / South Cambie)	Vancouver	V5Z	Lower Mainland	BC	Canada
Vancouver (East Mount Pleasant)	Vancouver	V5T	Lower Mainland	BC	Canada
Vancouver (Killarney)	Vancouver	V5S	Lower Mainland	BC	Canada
Vancouver (NE Downtown / Harbour Centre / Gastown / Yaletown)	Vancouver	V6B	Lower Mainland	BC	Canada
Vancouver (North Grandview-Woodlands)	Vancouver	V5L	Lower Mainland	BC	Canada
Vancouver (North Hastings-Sunrise)	Vancouver	V5K	Lower Mainland	BC	Canada
Vancouver (North West End / Stanley Park)	Vancouver	V6G	Lower Mainland	BC	Canada
Vancouver (NW Arbutus Ridge)	Vancouver	V6L	Lower Mainland	BC	Canada
Vancouver (NW Shaughnessy / East Kitsilano / Quilchena)	Vancouver	V6J	Lower Mainland	BC	Canada
Vancouver (Pacific Centre)	Vancouver	V7Y	Lower Mainland	BC	Canada
Vancouver (SE Kensington / Victoria-Fraserview)	Vancouver	V5P	Lower Mainland	BC	Canada
Vancouver (SE Kerrisdale / SW Oakridge / West Marpole)	Vancouver	V6P	Lower Mainland	BC	Canada
Vancouver (SE Oakridge / East Marpole / South Sunset)	Vancouver	V5X	Lower Mainland	BC	Canada
Vancouver (SE Riley Park-Little Mountain / SW Kensington / NE Oakridge / North Sunset)	Vancouver	V5W	Lower Mainland	BC	Canada
Vancouver (South Grandview-Woodlands / NE Kensington)	Vancouver	V5N	Lower Mainland	BC	Canada
Vancouver (South Hastings-Sunrise / North Renfrew-Collingwood)	Vancouver	V5M	Lower Mainland	BC	Canada
Vancouver (South Renfrew-Collingwood)	Vancouver	V5R	Lower Mainland	BC	Canada

Vancouver (South Shaughnessy / NW Oakridge / NE Kerrisdale / SE Arbutus Ridge)	Vancouver	V6M	Lower Mainland	BC	Canada
Vancouver (South West End)	Vancouver	V6E	Lower Mainland	BC	Canada
Vancouver (Strathcona / Chinatown / Downtown Eastside)	Vancouver	V6A	Lower Mainland	BC	Canada
Vancouver (SW Downtown)	Vancouver	V6Z	Lower Mainland	BC	Canada
Vancouver (UBC)	Vancouver	V6T	Lower Mainland	BC	Canada
Vancouver (Waterfront / Coal Harbour / Canada Place)	Vancouver	V6C	Lower Mainland	BC	Canada
Vancouver (West Fairview / Granville Island / NE Shaughnessy)	Vancouver	V6H	Lower Mainland	BC	Canada
Vancouver (West Kensington / NE Riley Park-Little Mountain)	Vancouver	V5V	Lower Mainland	BC	Canada
Vancouver (West Kitsilano / Jericho)	Vancouver	V6R	Lower Mainland	BC	Canada
Vancouver (West Mount Pleasant / West Riley Park-Little Mountain)	Vancouver	V5Y	Lower Mainland	BC	Canada
West Vancouver North	Vancouver	V7S	Lower Mainland	BC	Canada
West Vancouver South	Vancouver	V7V	Lower Mainland	BC	Canada
West Vancouver Southeast	Vancouver	V7T	Lower Mainland	BC	Canada
West Vancouver West	Vancouver	V7W	Lower Mainland	BC	Canada
Whistler	Whistler	V8E	Lower Mainland	BC	Canada
White Rock	White Rock	V4B	Lower Mainland	BC	Canada
Atlin Region (Atlin)		V0W	Other region	BC	Canada
Campbell River Central	Campbell River	V9W	Other region	BC	Canada
Campbell River Outskirts	Campbell River	V9H	Other region	BC	Canada
Cariboo and West Okanagan (100 Mile House)		V0K	Other region	BC	Canada
Castlegar		V1N	Other region	BC	Canada
Cedar		V9X	Other region	BC	Canada
Central Island (Chemainus)		V0R	Other region	BC	Canada
Central Okanagan and High Country (Revelstoke)		V0E	Other region	BC	Canada
Central Saanich		V8M	Other region	BC	Canada
Chilcotin (Alexis Creek)		V0L	Other region	BC	Canada
Comox		V9M	Other region	BC	Canada
Courtenay Central	Courtenay	V9N	Other region	BC	Canada
Courtenay Northern Outskirts	Courtenay	V9J	Other region	BC	Canada
Cranbrook		V1C	Other region	BC	Canada
Dawson Creek		V1G	Other region	BC	Canada
Duncan		V9L	Other region	BC	Canada
East Kootenays (Fernie)		V0B	Other region	BC	Canada
Esquimalt		V9A	Other region	BC	Canada
Fort St. John		V1J	Other region	BC	Canada
Highlands		V9B	Other region	BC	Canada

Inside Passage and the Queen Charlottes (Queen Charlotte City)		V0T	Other region	BC	Canada
Juan de Fuca Shore (Sooke)		V0S	Other region	BC	Canada
Kamloops Central and Southeast	Kamloops	V2C	Other region	BC	Canada
Kamloops North	Kamloops	V2H	Other region	BC	Canada
Kamloops Northwest	Kamloops	V2B	Other region	BC	Canada
Kamloops South and West	Kamloops	V2E	Other region	BC	Canada
Kamloops Southwest		V1S	Other region	BC	Canada
Kelowna Central	Kelowna	V1Y	Other region	BC	Canada
Kelowna East	Kelowna	V1P	Other region	BC	Canada
Kelowna East Central	Kelowna	V1X	Other region	BC	Canada
Kelowna North	Kelowna	V1V	Other region	BC	Canada
Kelowna Southwest	Kelowna	V1W	Other region	BC	Canada
Kelowna West	Kelowna	V1Z	Other region	BC	Canada
Kimberley		V1A	Other region	BC	Canada
Kitimat		V8C	Other region	BC	Canada
Ladysmith		V9G	Other region	BC	Canada
Lower Skeena (Port Edward)		V0V	Other region	BC	Canada
Merritt		V1K	Other region	BC	Canada
Metchosin		V9C	Other region	BC	Canada
Nanaimo Central	Nanaimo	V9S	Other region	BC	Canada
Nanaimo North	Nanaimo	V9T	Other region	BC	Canada
Nanaimo Northwest	Nanaimo	V9V	Other region	BC	Canada
Nanaimo South	Nanaimo	V9R	Other region	BC	Canada
Nelson		V1L	Other region	BC	Canada
North Central Island and Bute Inlet Region (Gold River)		V0P	Other region	BC	Canada
Northern British Columbia (Fort Nelson)		V0C	Other region	BC	Canada
Oak Bay North	Oak Bay	V8R	Other region	BC	Canada
Oak Bay South	Oak Bay	V8S	Other region	BC	Canada
Omineca and Yellowhead (Smithers)		V0J	Other region	BC	Canada
Parksville		V9P	Other region	BC	Canada
Penticton		V2A	Other region	BC	Canada
Port Alberni		V9Y	Other region	BC	Canada
Powell River		V8A	Other region	BC	Canada
Prince George East Central	Prince George	V2L	Other region	BC	Canada
Prince George North	Prince George	V2K	Other region	BC	Canada
Prince George South	Prince George	V2N	Other region	BC	Canada
Prince George West Central	Prince George	V2M	Other region	BC	Canada
Prince Rupert		V8J	Other region	BC	Canada
Qualicum Beach		V9K	Other region	BC	Canada

Quesnel		V2J	Other region	BC	Canada
Saanich Central	Saanich	V8Z	Other region	BC	Canada
Saanich East	Saanich	V8N	Other region	BC	Canada
Saanich North	Saanich	V8Y	Other region	BC	Canada
Saanich South	Saanich	V8X	Other region	BC	Canada
Saanich Southeast	Saanich	V8P	Other region	BC	Canada
Saanich West		V9E	Other region	BC	Canada
Salmon Arm		V1E	Other region	BC	Canada
Saltspring Island		V8K	Other region	BC	Canada
Sidney		V8L	Other region	BC	Canada
Sooke		V9Z	Other region	BC	Canada
South Okanagan (Summerland)		V0H	Other region	BC	Canada
Terrace		V8G	Other region	BC	Canada
Trail		V1R	Other region	BC	Canada
Upper Columbia Region (Golden)		V0A	Other region	BC	Canada
Vernon Central	Vernon	V1T	Other region	BC	Canada
Vernon East	Vernon	V1B	Other region	BC	Canada
Vernon West	Vernon	V1H	Other region	BC	Canada
Victoria Central British Columbia Provincial Government	Victoria	V8W	Other region	BC	Canada
Victoria North	Victoria	V8T	Other region	BC	Canada
Victoria South	Victoria	V8V	Other region	BC	Canada
West Kootenays (Rossland)		V0G	Other region	BC	Canada
Westbank		V4T	Other region	BC	Canada
Williams Lake		V2G	Other region	BC	Canada
Winfield		V4V	Other region	BC	Canada

Table A2: Change-in-estimate HR ratio percent change for average NO_2

Covariates remaining in model	Variable removed	Percent change
15	Maternal history	-0.04%
14	PA	0.26%
13	Fruit	-0.10%
12	Vegetables	-0.31%
11	Contraceptives	0.12%
10	Ethnicity	0.85%
9	Smoking	1.55%
8	Education	-1.22%
7	Birth	-0.08%
6	Alcohol	0.31%
5	Income	3.62%
4	Age	-0.50%

Final model: BMI, material deprivation and social deprivation
* Percent change based off of a 1-IQR increase

Table A3: Change-in-estimate HR ratio percent change for average NO_2

Covariates remaining in model	Variable removed	Percent change*
15	Education	-0.15%
14	Birth	0.29%
13	Fruit	-0.02%
12	Ethnicity	0.21%
11	Vegetable	0.21%
10	Contraceptives	-0.38%
9	Smoking	-0.34%
8	Maternal history	0.58%
7	Alcohol	-0.51%
6	Age	-2.82%
5	Income	0.79%
4	PA	3.25%

Abbreviations: BMI, body mass index; PA: physical activity
Final model: BMI, material deprivation and social deprivation
* Percent change based off of a 1-IQR increase

Table A4: Change-in-estimate HR ratio percent change for walkability

Covariates remaining in model	Variable removed	Percent change*
15	Vegetable	-0.11%
14	Maternal history	0.10%
13	Ethnicity	0.33%
12	Fruit	-0.27%
11	Contraceptives	0.12%
10	Alcohol	0.13%
9	Smoking	0.82%
8	Age	-0.45%
7	Birth	0.42%
6	Education	-2.55%
5	Income	1.58%

Abbreviations: BMI: body mass index; PA: physical activity
Final model: BMI, PA, material deprivation and social deprivation
* Percent change based off of a 1-quintile increase

Table A5: Change-in-estimate HR ratio percent change for green space (NDVI)

Covariates remaining in model	Variable removed	Percent change*
15	Vegetable	0.14%
14	Ethnicity	-0.08%
13	Maternal history	0.21%
12	Smoking	0.05%
11	Contraceptives	-0.89%
10	Fruit	0.33%
9	PA	-1.25%
8	Age	0.17%
7	Income	-0.67%
6	Material deprivation	-0.27%
5	Education	-0.27%
4	Birth	-1.23%
3	BMI	-0.02
2	Alcohol	-0.05

Abbreviations: BMI: body mass index; PA: physical activity
Final model: social deprivation
* Percent change based off of a 1-IQR increase

Table A6: Change-in-estimate HR ratio percent change for average green space (NDVI)

Covariates remaining in model	Variable removed	Percent change*
15	Smoking	0.07%
14	Contraceptives	-0.13%
13	Vegetables	0.15%
12	Ethnicity	-0.17%
11	Fruit	0.62%
10	Alcohol	-0.02%
9	Income	0.40%
8	Maternal history	-0.01%
7	Education	-1.38%
6	Age	0.43%
5	Birth	-1.46%
4	Material deprivation	1.88%
3	PA	-0.48%

Abbreviations: BMI: body mass index; PA: physical activity
Final model: BMI and social deprivation
* Percent change based off of a 1-IQR increase