PHYSICAL ACTIVITY ACROSS THE LIFE COURSE AND RISK OF PRE- AND POST-MENOPAUSAL BREAST CANCER

by

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Abstract

Background: Moderate-to-vigourous intensity physical activity (MVPA) is among the few modifiable factors known to reduce breast cancer risk. However, the independent effects of leisure-time, household, and occupational MPVA by age period across the life course remain poorly understood. Whether these effects differ by menopausal status and by tumour subtypes defined by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) is unknown. An understanding of these issues will help advance policy and public health action targeting breast cancer prevention through physical activity.

Methods: A case-control study of 1,011 incident breast cancer cases and 1,014 cancer-free controls aged 40-80 years was conducted from 2006-2010 in Vancouver, British Columbia (BC). Lifetime leisure-time, household, and occupational MVPA were assessed by questionnaire and mean MET-hrs/week of each were calculated for age periods 12-17, 18-34, 35-49, and ≥50 years and the total lifetime. Odds ratios for pre- and post-menopausal breast cancer risk associated with each activity domain across age periods were estimated using unconditional logistic regression, and odds ratios for risks of ER/PR-defined and ER/PR/HER2-defined breast tumours were estimated using unconditional polytomous logistic regression.

Results: Among post-menopausal women, lifetime leisure-time and household MVPA reduced breast cancer risk by approximately 50% at volumes equal to 3 hours per week of running and 21 hours per week of active household work. MVPA reduced risk at all age periods across the life course, particularly during adulthood. Effects of leisure-time MVPA appeared restricted to HER2- tumours. Household MVPA reduced risk for ER/PR+ tumours, regardless of HER2 status. MVPA

was not associated with pre-menopausal breast cancer risk, except occupational MVPA performed during ages 18-34 was associated with a doubling in risk.

Conclusions: MVPA is a lifestyle factor women may engage in to reduce post-menopausal breast cancer risk. Results suggest HER2 may be implicated in anti-breast carcinogenic effects of leisure-time MVPA. Increased risk associated with occupational MVPA may be due to occupational exposures related to job intensity. Further research on specific aspects of weekly MVPA energy expenditure dose required to reduce breast cancer risk will aid in refining physical activity recommendations for breast cancer prevention.

Co-Authorship

This thesis is the work of Lindsay Kobayashi in collaboration with her supervisors, Drs. Kristan Aronson and Ian Janssen. The Molecular Epidemiology of Breast Cancer study is led by two co-principal investigators, Drs. Kristan Aronson and John Spinelli. Data management and statistical analysis for the thesis was performed by Lindsay Kobayashi with guidance from Drs. Kristan Aronson and Ian Janssen. Interpretation of results and writing of the thesis was performed by Lindsay Kobayashi, with editorial feedback from Drs. Kristan Aronson, Ian Janssen, Harriet Richardson, Caroline Lohrisch, Sandip SenGupta, and John Spinelli.

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List of Abbreviations

ALPHA	Alberta Trial of Physical Activity and Breast Cancer Prevention
ANOVA	Analysis of variance
BC	British Columbia
BMI	Body mass index
BRCA1/2	Breast cancer susceptibility genes 1 & 2
CBCRA	Canadian Breast Cancer Research Alliance
CI	Confidence interval
CIHR	Canadian Institutes for Health Research
CRP	C-reactive protein
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen receptor
FISH	Fluorescence *in situ* hybridization
GPAQ	Global Physical Activity Questionnaire
HER2	Human epidermal growth factor receptor 2
HRT	Hormone replacement therapy
IGF-1	Insulin-like growth factor-1
IGFBP	Insulin-like growth factor binding protein
IHC	Immunohistochemistry
IL-6	Interleukin-6
MEBC	Molecular Epidemiology of Breast Cancer Study
MET	Metabolic equivalent
MVPA	Moderate-to-vigourous intensity physical activity
NHANES	National Health and Nutrition Examination Survey
NIH-AARP	National Institutes of Health – American Association of Retired Persons
OR	Odds ratio
PA	Physical activity
PR	Progesterone receptor
SAS	Statistical analysis software
SD	Standard deviation
SHBG	Sex hormone binding globulin
SMP BC	Screening Mammography Program of BC
TNM	Tumour-Node-Metastasis
WHO	World Health Organization

Chapter 1

Introduction

1.1 General Introduction

Breast cancer is the most common incident cancer and the second leading cause of cancer death among Canadian women (1). In 2011, the estimated age-standardized incidence rate for female breast cancer in Canada was 102 per 100,000 population and the age-standardized mortality rate was 21 per 100,000 (1). Etiology, prognosis, and survival differ between pre- and post-menopausal women, with pre-menopausal breast cancers more likely to be genetic in origin with worse prognosis and survival than post-menopausal breast cancers (1–3). Subsequently, breast cancer is often accepted as two distinct diseases between menopausal groups. Moreover, with the advent of molecular and genetic breast tumour profiling, breast cancer is becoming increasingly complex and several molecular subtypes may in fact exist.

Understanding of modifiable breast cancer risk factors among pre- and post-menopausal women and for distinct molecular breast tumour subtypes is crucial for the reduction of preventable cases through policy and public health action. Most known risk factors for breast cancer are reproductive and/or hormonal in nature and not easily modified. Moderate-to-vigourous intensity physical activity (MVPA) is one of the few modifiable factors accepted as protective against breast cancer (4–6). The recent World Health Organization public health recommendations on physical activity are that adults accumulate at least 150 minutes per week of moderate intensity activity, or 75 minutes per week of vigourous intensity activity, or an equivalent combination of the two to reduce the risk for several chronic diseases including

breast cancer (6). The Public Health Agency of Canada, the American Cancer Society, and the American Centers for Disease Control and Prevention have adopted similar recommendations (4,6–8). The most recent epidemiologic review of physical activity and breast cancer risk, a narrative review published in 2011, found an average breast cancer risk reduction of 25% among women with the highest vs. lowest levels of MVPA in 73 studies from various global locations (5). A 2007 review found risk reductions for breast cancer of 20-80% among post-menopausal women, which were attenuated to 15-20% when pre-menopausal women were included (9), while the 2011 review found an average risk reductions of 31% among post-menopausal and 27% among pre-menopausal women for the most vs. the least physically active women (5).

Despite the amount of research in this topic area, several key questions about the relationship between physical activity and breast cancer remain unknown: Firstly, what are the independent effects and relative importance of MVPA performed in different domains of life, such as leisure-time, household work, and occupational work? These domains, representing different activity types (e.g., aerobic exercise during leisure-time, brisk walking and repetitive movements during household and occupational work, all under varying degrees of voluntary participation and stress), have rarely been examined independently of one another over the life course (10–13). Second, do the specific age period(s) across the life course where MVPA is accrued influence the reduction in breast cancer risk? Whether physical activity acts in a time-sensitive manner, similar to other hormonal risk factors, is not well understood (14). Thirdly, does the relationship between MVPA and breast cancer risk differ depending on breast tumour subtype defined by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)? Emerging, yet inconsistent evidence indicates risk heterogeneity by tumour subgroup may exist (5).

1.2 Study Design Overview

A CIHR/CBCRA-funded case-control study ("Molecular Epidemiology of Breast Cancer" (MEBC)) was conducted in Vancouver, British Columbia (BC) among women 40 to 80 years of age with no previous cancer history (except non-melanoma skin cancer). From 2006-2010, eligible incident breast cancer cases were recruited from the BC Cancer Registry, with controls randomly selected from cancer-free women enrolled in the BC Screening Mammography Program and residing in the same geographic area. 1,011 incident cases and 1,014 controls were recruited, with response rates of 54% for cases and 57% for controls. All consenting participants completed a detailed questionnaire and most provided a blood sample and medical records.

1.3 Objectives

1. To describe lifetime MVPA energy expenditure cumulatively and over four age periods of exposure for pre- and post-menopausal cases and controls;
2. To determine the relationship between lifetime MVPA energy expenditure cumulatively and over four age periods of exposure and breast cancer risk separately within pre- and post-menopausal women; and,
3. To determine the relationship between lifetime MVPA energy expenditure cumulatively and over four age periods of exposure and risk of ER+ and/or PR+ and ER-/PR- breast tumours, and in an exploratory analysis, ER+ and/or PR+/HER2+, ER+ and/or PR+/HER2-, ER-/PR-/HER2+, and ER-/PR-/HER2- breast tumours, separately within pre- and post-menopausal women.

1.4 Thesis Organization

This is a manuscript based thesis that conforms to the regulations outlined by the *Queen's University School of Graduate Studies and Research*. The second chapter of this thesis is a literature review covering the current state of knowledge regarding: major risk factors for breast cancer; ER/PR-defined and ER/PR/HER2-defined breast tumour subtypes; physical activity measurement in epidemiologic research; and, physical activity and breast cancer risk with respect to energy expenditure dose, activity domain, biologically effective age periods, effect modification by menopausal status, and effects on ER/PR-defined and ER/PR/HER2-defined tumour subtypes. The third chapter will detail the methodology of this research. Chapters four and five consist of the two manuscripts for publication of this research. Chapter six presents additional results not found in the manuscripts. Chapter seven is a discussion of main findings including implications for future research. Extra material may be found in appendices at the end.

1.5 Contribution

This thesis will address several unknown and uncertain aspects of the relationship between MVPA and pre- and post-menopausal breast cancer risk. This research will determine the independent effects of leisure-time, household, and occupational MVPA across the life course on risk for overall breast cancer and breast tumour subtypes among pre- and post-menopausal women. Knowledge generated from this research will contribute toward better understanding the relationship between physical activity and breast cancer risk, and will have potential for use in health policy targeting physical activity for breast cancer prevention.

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Chapter 2

Literature Review

2.1 Introduction

Breast cancer is the most commonly diagnosed malignancy and the second most common cause of cancer death among women in Canada (1). In 2011, the estimated age-standardized incidence rate for female breast cancer in Canada was 102 per 100,000 and the age-standardized mortality rate was 21 per 100,000 (1). Despite its relatively common frequency among women, approximately 60% of breast cancer etiology is unknown and several established factors comprising the known fraction of etiology are not easily modifiable (2,3). Moderate-to-vigourous intensity physical activity (MVPA) is among the few factors that reduce breast cancer risk, with the most recent review in 2011 finding an average risk reduction of 25% when comparing the most vs. the least physically active groups of women (4).

Despite current knowledge, several uncertainties remain regarding the relationship between MVPA and breast cancer. The independent effects of leisure-time, household, and occupational MPVA by age period across the life course remain poorly understood. Whether these effects further differ across breast tumour subtypes defined by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) is unknown (4,5). Further, how all of these factors may differ by menopausal status is not well understood. An understanding of these issues will help advance policy and public health action targeting breast cancer prevention through physical activity.

This chapter will review the current state of knowledge regarding the relationship between MVPA and breast cancer risk. First, key definitions will be provided. Etiology and

pathology of breast cancer and ER/PR-defined and ER/PR/HER2-defined breast tumour subtypes will be briefly discussed. Next, physical activity and its measurement in epidemiologic research will be discussed, followed by an in-depth review of MVPA and breast cancer risk. Potential confounders will be reviewed, and the chapter will conclude with the rationale for this thesis.

2.2 Key Definitions

Breast cancer is a form of cancer that begins in breast tissue (6). Breast cancer is routinely classified in the clinical setting by the positive or negative status of the *estrogen receptor* (*ER*), *progesterone receptor* (*PR),* and *human epidermal growth factor receptor 2* (*HER2*; also known as Erb-b-2) because of their prognostic importance (7). In this thesis, the following breast tumour subtypes will be examined: ER+ and/or PR+ (referred to as ER/PR+ from here on) and ER-/PR-, which will then be further subdivided by HER2 status into ER+ and/or PR+/HER2+ (referred to as ER/PR+/HER2+ from here on); ER+ and/or PR+/HER2- (referred to as ER/PR+/HER2- from here on); ER-/PR-/HER2+; and ER-/PR-/HER2-.

Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure (8). Physical activity *energy expenditure dose* is the combination of frequency, duration, and intensity of physical activity performed, typically described as the amount of time spent engaging in physical activity of a specific intensity during a specified unit of time (often day or week) (9). *Moderate-to-vigourous intensity physical activity* (*MVPA)* refers to physical activity at a relative intensity of 55-90% maximum heart rate, or ≥3 times resting energy expenditure, and includes activities such as brisk walking, heavy housework, jogging, or cycling (10). *Physical activity domain* refers to the domain of daily activities where physical activity is performed, such as recreational and leisure-time activity, household work, or occupational work. The *biologically effective age period*, with respect to physical activity and

breast cancer, is the period(s) of time in life where performance of physical activity is associated with reduced breast cancer risk and biologic anti-cancer effects of physical activity during this time(s) can be inferred.

Menopause is the stage in life where a woman's periods naturally cease, usually between the ages of 45 and 55 (11). Menopause may also be induced by oophorectomy (removal of the ovaries) or through chemotherapy or hormone therapy treatment for cancer (11). Prior to menopause, a woman is said to be *pre-menopausal*, while after menopause, a woman is said to be *post-menopausal*. Menopausal status modifies the effects of physical activity on breast cancer risk, where the biologic effects of MVPA relevant to breast carcinogenesis are hypothesized to differ between menopausal groups (12).

2.3 Breast Cancer

Breast cancer is the most commonly diagnosed malignancy and the second most common cause of cancer death among women in Canada (1). The lifetime probability of developing breast cancer for Canadian women is estimated to be one in nine, and the lifetime probability of mortality due to breast cancer is one in 29 (1). Fifty three percent of breast cancers occur in women aged 50 to 69, 19% occur in women under age 50, and 28% in women over age 69 (1). Five-year relative survival is significantly worse among women diagnosed between ages 15-39 and 80-99 compared to women aged 40-79 (1). Breast cancer is associated with negative economic burden: on average, a woman in Canada diagnosed with breast cancer can expect to lose 10% of her household income over the course of the illness and one in five women are forced to quit their previous job because of their diagnosis (13).

Female breast cancer may begin in the milk duct (ductal) tissue or the lobular milk-producing (lobular) tissue of the breast, and when confined to either of these tissues is termed

ductal or lobular carcinoma *in situ*, respectively (14). The majority (80-90%) of breast tumours begin in ductal tissue, while 7-8% begins in lobular tissue (15). Other rarer forms of breast cancer may begin outside of the ductal or lobular breast tissue (6). Carcinoma *in situ* is the earliest stage of breast cancer (stage 0), while cancer spread outside of ductal or lobular tissue is said to be invasive and is staged (I through IV) depending on primary tumour size (T), regional lymph node involvement (N), and presence of distant metastases (M), according to the TNM system (14). The most important clinical prognostic indicators for breast cancer are *in situ* versus invasive status, and among invasive tumours, TNM stage and ER, PR, and HER2 statuses (16).

Established breast cancer risk factors include: increasing age, primary family history of breast cancer, BRCA1/2 gene polymorphisms, history of previous benign breast disease, history of cancer in the other breast, radiation exposure to the chest, early age at menarche, nulliparity, late age at first birth, diethylstilbestrol exposure during pregnancy, oral contraceptive use, alcohol use, obesity, a fatty diet and physical inactivity (3,6,17,18). The degree to which some of these factors alter the risk of developing breast cancer is contingent on menopausal status. Obesity reduces breast cancer risk among pre-menopausal women and increases risk among post-menopausal women (3). Late age at menopause and use of hormone replacement therapy increase breast cancer risk among post-menopausal women (3). Physical activity has a stronger protective effect on post-menopausal women than on pre-menopausal women (12).

Although breast cancer is often discussed as a single disease, it is far more complex in reality. Etiology, prognosis, and survival differ between pre- and post-menopausal women (1,18). Subsequently, breast cancer is often accepted to be two distinct diseases between menopausal groups. Moreover, with the advent of molecular and genetic breast tumour profiling, breast cancer is becoming increasingly complex and several subtypes may exist (19).

2.4 ER/PR-defined and ER/PR/HER2-defined Breast Tumour Subtypes

Human breast tumours were first classified using genetic profiling in the year 2000, when four breast tumour subtypes were identified based on the presence or absence of several molecular tumour markers (19). This thesis focuses on similar subtypes based on the three of these tumour markers that are routinely utilized in clinical practice: the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). Epidemiologic studies of breast cancer have often examined etiologic heterogeneity of breast tumours based on ER and/or PR status, while further examination by HER2 status is more recent (20). When examined by HER2 status, the four tumour subtypes of interest are: ER/PR+/HER2+; ER/PR+/HER2-; ER-/PR-/HER2+; and ER-/PR-/HER2- (7,20,21). These subtypes are an approximation to the original subtypes identified in 2000 through genetic profiling, as the original subtypes utilize molecular markers not tested for in routine clinical practice.

Prognostic heterogeneity by ER, PR, and HER2 tumour status is well-documented (20-23). Approximately 80% of breast cancers are ER/PR+ and 20% are ER-/PR- (24). Approximately 65% of breast cancers are ER/PR+/HER2-, 15% are ER/PR+/HER+, 7% are ER-/PR-/HER2+, and 13% are ER-/PR-/HER2- (24). Responsive to the targeted therapy tamoxifen, ER+ tumours are associated with a more favourable prognosis than ER- tumours (7,22). HER+ tumours are more aggressive than HER2- tumours, and are responsive to the targeted therapy trastuzumab (7,22). ER-/PR-/HER2- tumours ("triple negative") do not respond to these therapies, and thus are associated with a worse prognosis than receptor-positive tumours, representing a significant clinical challenge (22,23).

Etiologic heterogeneity of breast tumours by ER status is accepted (PR status is correlated with ER status and often examined synonymously with ER status in epidemiologic

research) (20). Known associations include: increased ER+ breast cancer risk with nulliparity, early menarche, hormone replacement therapy use, older age, and white race, and increased risk for ER- breast cancer with younger age, non-white race, and BRCA1 gene mutations (25-29).

The relevance of HER2 as an additional marker of etiologic tumour heterogeneity is uncertain (20), although recent epidemiological evidence indicates that ER/PR/HER2-defined breast tumour subtypes do not share the same risk factors previously understood to apply to all breast cancer. These risk factors include age, race, and reproductive factors such as age at menarche, parity, and oral contraceptive use (23,30-39). In these relatively few studies, the most consistent association is a higher risk for triple-negative breast cancer among African-American women (32-35) and among women under age 50 (33,34,40,41). Small sample sizes of tumour subtypes in some studies, inaccuracies in HER2 status classification, and methodological disparities between studies may have contributed to inconsistent risk estimates (20).

2.5 Physical Activity

When assessing the relationship between physical activity and cancer risk in epidemiologic research, the biological effects of physical activity that influence carcinogenesis are the true exposure of interest. As a proxy for these biological effects, observational epidemiologic research often measures physical activity energy expenditure dose: the combination of the frequency, duration, and intensity of activity performed (9). Alone, physical activity frequency and duration comprise “volume” of activity, often described as the amount of time spent per week (or other unit of time; although weeks will be the unit of analysis in this thesis) engaging in physical activity. Intensity must be combined with the volume measure to determine the energy expenditure dose, which in simpler terms refers to how many calories are burned through physical activity. Research in breast cancer and other chronic diseases typically

focuses on physical activity of a moderate or vigourous intensity. In the context of breast cancer (as well as several other cancers and chronic diseases), the timing in life when physical activity is performed is of concern due to the cancer's long and mostly unknown latency period (9).

2.5.1 Physical Activity Measurement in Epidemiologic Research

Most observational epidemiologic studies examining physical activity in relation to cancer risk have used self-report questionnaires for retrospective physical activity assessment (e.g. past month for prospective cohort studies, or physical activity 20 years ago for case-control studies). Recall, and in turn, reliability, are important concerns with physical activity questionnaires. Physical activity recall is shown to improve (higher associated test-retest correlations) as intensity increases from light to vigourous (42,43). The pilot-test of the Total Lifetime Physical Activity Questionnaire found respective Pearson's *r* values of 0.38, 0.65, and 0.85 for lifetime light, moderate, and vigourous intensity physical activity reported in two interviews 6-8 weeks apart among 115 women recruited from a breast screening program (43). Similarly, a prospective study compared reported leisure-time physical activity at baseline with recall of the same activity 10 years later, finding Pearson's *r* values of 0.25, 0.32, and 0.44 for light, moderate, and vigourous intensity activity, respectively (42).

With the Total Lifetime Physical Activity Questionnaire, recall of lifetime physical activity, regardless of domain, is more accurate than recall of activity in the past reference year (Pearson's *r* for lifetime activity ranges from 0.72 for exercise/sports to 0.87 for occupational activity; Pearson's *r* for reference year activity ranges from 0.50 for household activity to 0.70 for occupational activity), suggesting that recall through long-term generic memory is more accurate than through episodic memory (43,44).

In general, retrospective physical activity self-report is associated with over-reporting of activity duration and intensity (45). In a study of Californian men and women, re-questioning of physical activity performed and originally questioned about 11 years prior resulted in a 41% increase in reported weekly energy expenditure (46). When recall accuracy and/or over-reporting are differential between cases and controls in case-control research, recall bias is introduced into results. When recall errors are non-differential between cases and controls effect estimates become biased toward the null and underestimate the true effects.

Further issues hindering accuracy of physical activity questionnaires include the inherent difficulty of quantitatively assessing physical activity due to its subjective and individual nature (47). Physical activity reporting varies by age and gender (48). Individual perceptions of intensity depend on factors such as athletic fitness, existing fatigue, and environmental conditions such as heat and humidity (47,48). Hence, physical activity reporting can be highly variable within populations. These matters are complicated by the difficulty in validating physical activity questionnaires, as doing so requires prospective access to a cohort with objective measurements, such as pedometer or accelerometer data: when lifetime physical activity is of interest, validation would require follow-up of a cohort over a lifetime (47). These issues have contributed to somewhat inconsistent risk estimates in the epidemiological literature on physical activity and breast cancer. Reliable and valid questionnaire design is thus essential to high-quality retrospective physical activity assessment.

2.5.2 Metabolic Equivalent Scoring

Physical activity energy expenditure dose measured using questionnaires may be operationalized into a quantitative measure using metabolic equivalent scoring, or, MET scoring (49). MET scores are defined as the ratio of the calculated metabolic rate for a specific activity

compared to resting metabolic rate (49). The resting metabolic rate, the reference, corresponds to a MET score of 1.0, and is equivalent to sitting still at rest (49). All other physical activities are assigned scores based on energy expenditure relative to this referent, and these scores are compiled in the MET Compendium (48,49). For example, the rate of metabolic energy expenditure while running at 5 miles/hour has been assessed to be eight times the rate while sitting at rest, and thus running at 5 miles/hour is assigned a MET score of 8.0. MET values in the Compendium range between 0.9 (sleeping) and 18.0 METs (running at 10.9 miles/hour) (48). Ranges of MET scores have been categorized to define intensity levels, shown in Table 2.1.

In the research setting, MET scores from the Compendium are applied to collected data on physical activity frequency and duration to create a measure for energy expenditure dose, usually in MET-mins or MET-hrs. MET scoring allows several activities at different intensities and durations to be summed into a total weekly or daily MET-mins or MET-hrs value. For example, an individual who runs at 5 miles/hour (MET score=8.0) for 1 hour, 3 days per week and walks briskly at work (MET score=3.3) for 30 minutes per day, 5 days per week would accumulate a total of 32.25 MET-hrs (1 hour*3 days/week*8.0 METs + 0.5 hours*5 days/week*3.3 METs) or 1,935 MET-mins (60 mins*3 days/week/8.0 METs + 30 mins*5 days/week*3.3 METs) per week.

One MET is equivalent to consuming 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (3.5 mL of oxygen per kilogram body weight per minute), which in turn is equivalent to expending 1 $kcal \cdot kg^{-1} \cdot hr^{-1}$ (1 kilocalorie per kilogram body weight per hour) of energy (49). These absolute energy expenditure values were calculated based on oxygen consumption calculations for healthy, 40 year old males with an average body mass of 70 kg, and subsequently may not correspond to absolute energy expenditure for females of varying ages, fitness levels, and body weights, such as in the present study population (50). However, the objectives of this thesis are not to determine absolute

energy expenditure and METs are accepted as useful and valid for purposes of comparing relative energy expenditure within populations (43,49).

Table 2.1 Physical activity intensity according to MET scores (adapted from (10))	
MET Score	**Physical Activity Intensity and Description**
1.0 < 1.6	**Sedentary**: activities that usually involve sitting or lying and that have little additional movement and a low energy requirement; requires < 40% maximum heart rate
1.6 < 3.0	**Light**: aerobic activities that do not cause noticeable changes in breathing rate; an intensity that can be sustained for at least 60 minutes; requires 40 < 55% maximum heart rate
3.0 < 6.0	**Moderate**: an aerobic activity that is able to be conducted whilst maintaining a conversation uninterrupted; an intensity that may last between 30 and 60 minutes; requires 55 < 70% maximum heart rate
≥ 6.0	**Vigourous**: an aerobic activity in which a conversation generally cannot be maintained uninterrupted; an intensity that may last up to about 30 minutes; beyond 9 METS, an intensity that generally cannot be sustained for longer than about 10 minutes; requires 70 < 90% of maximum heart rate

2.6 Physical Activity and Breast Cancer Risk

The relationship between physical activity and breast cancer risk has been investigated in over 90 epidemiological studies (4). In a 2011 narrative review of 73 studies on physical activity and breast cancer risk, only 29 found statistically significant risk reductions when comparing the highest vs. lowest physical activity groups (4). This inconsistency amongst effect estimates for the relationship between physical activity and breast cancer risk is likely in part due to the wide range of methodologies used in previous research to measure this relationship, as well as varying study designs, sample sizes, and study populations. The average effect estimate of all studies included in the review was a risk reduction of 25% when comparing the most to the least active women in each study (4). Similarly, a 2008 review observed an average risk reduction of 25-30% with increased physical activity in 47 of 62 studies examined (51).

2.6.1 Physical Activity Intensity and Breast Cancer Risk

As shown in Table 2.1, physical activity intensity is classified as sedentary, light, moderate, or vigourous. This thesis will focus on moderate-to-vigourous intensity physical activity (MVPA), that is, physical activity corresponding to a MET score of 3.0 or higher. Most epidemiologic evidence for physical activity and breast cancer risk pertains to MVPA, while light intensity activity has rarely been adequately examined (4). Although methods for defining and measuring physical activity intensity are inconsistent in the literature, MVPA appears to have a stronger effect on breast cancer risk than light intensity activity.

In the 2003 San Francisco Bay Area Breast Cancer Study, pre- and post-menopausal women in the highest tertiles of moderate intensity activity had reduced breast cancer risks (respective ORs = 0.67; 95% CI: 0.46-0.96 and 0.74; 95% CI: 0.59-0.96), which were attenuated toward the null when light intensity activity was included (52). Similarly, in a large case-control study in Alberta, Canada, lifetime moderate intensity activity reduced breast cancer risk among post-menopausal women in the highest quartile (OR=0.59; 95% CI: 0.42-0.83) with no effect observed for light intensity activity (53). No effect was observed for pre-menopausal women at either intensity (53). The prospective NIH-AARP Diet and Health study of 118,899 post-menopausal U.S. women found no association between light intensity leisure-time activities performed at any lifetime period and breast cancer risk, while MVPA in the past 10 years was associated with a 16% reduction in breast cancer risk (RR=0.84; 95% CI: 0.76-0.93) (54).

Biomarker studies also show that MVPA appears more efficacious than light intensity activity in producing the biologic effects thought responsible for the reduced breast cancer risk associated with physical activity. MVPA objectively measured in the Alberta Breast Cancer Prevention Trial and in the U.S. National Health and Nutrition Examination Survey 2003-2006

(NHANES) was found to reduce adiposity, sex hormone levels, improve insulin resistance, and to have anti-inflammatory effects, all of which are thought to reduce breast cancer risk (55-59) (see section 2.6.6 for more details). Less evidence exists for these effects with light intensity activity, which has not been investigated for association with biomarkers of breast cancer risk outside of NHANES (59). Light intensity activity in NHANES was associated with the same biomarkers of breast cancer risk as MVPA, although with a lesser strength (59).

2.6.2 Physical Activity Energy Expenditure Dose and Breast Cancer Risk

A dose-response relationship has generally been observed for MVPA energy expenditure dose where increasing activity leads to greater risk reductions (4,5,51). A 2007 systematic review found a 6% decrease ($\beta_{activity}$=-0.056; 95% CI: -0.084 to -0.029) in risk for breast cancer for each additional hour of leisure-time MVPA performed per week (60). The World Health Organization, the American Cancer Society, and the Public Health Agency of Canada recommend 150 minutes/week of MVPA for adults for reduction in risk of various health outcomes including breast cancer (61-63). Some evidence indicates a higher weekly volume of MVPA may be required to reduce breast cancer risk. In a 2003 narrative review, I-Min Lee observed that at least 30-60 minutes/day (equal to 210-420 minutes/week) of MVPA are required to reduce breast cancer risk, based on prospective findings of a Norwegian cohort and the U.S. Women's and Nurses' Health Studies (64). Another narrative review has concluded that 4-7 hours/week (240-420 minutes/week) of MVPA are required to reduce breast cancer risk (5). In the U.S. NIH-AARP Diet and Health Study, leisure-time MVPA was associated with a 16% reduction in breast cancer risk at >7 hours/week (>420 minutes/week), with no effect at lower weekly doses (54). Confirmation of the weekly MVPA dose required to reduce breast cancer risk will be important for physical activity recommendations for breast cancer prevention.

2.6.3 Physical Activity Domain and Breast Cancer Risk

Although most epidemiologic research has focused on sport/recreational/leisure-time physical activity, women perform physical activity in all areas of life. The 1998 Statistics Canada General Social Survey found that, aside from sleeping, Canadian women over age 15 spent the largest proportion of their time engaged in occupational and household work, with 3.4 and 4.4 hours per day on average, respectively (65). By contrast, women spent only 0.75 hours/day on average engaged in active leisure activities (65). Initial results from the Tomorrow Project cohort in Alberta, Canada support these findings, showing that, on average, women engaged in occupational work for 3.7 hours per day, household work for 3.4 hours per day, and leisure-time activities for 0.8 hours per day (66). Thus, energy expended during occupational and household work is of interest because of the large proportion of time spent by women in both domains.

Most studies examining physical activity and breast cancer risk have not accounted for physical activity from different domains, and subsequently some results may be subject to uncontrolled confounding if activities in different settings are related to one another. Previous research has found that women who engage in high levels of occupational physical activity also engage in high levels of household activity (67). Results from the Alberta Tomorrow Project show that hours per week of MVPA spent engaging in household, occupational, and leisure time activities increase together as total physical activity level increases (66). Failure to account for all sources of physical activity may also result in misclassification of physical activity exposure.

Six studies have investigated simultaneous effects of leisure-time, household, and occupational activity independent of one another (52,68-72). Of these, two attempted to stratify by intensity, with one incorrectly classifying MVPA as a MET score ≥4.5 (71) and another

analysed moderate intensity activities only (52). These six studies generally show protective effects of varying magnitude, although results are inconsistent by domain and some are null.

The first, a large case-control study conducted in Alberta, Canada in 2001 found an OR of 0.70 (95% CI: 0.52-0.95) among post-menopausal women for the highest vs. lowest MET-hrs/week quartile (all intensities combined) of lifetime physical activity from all three domains combined (68). The authors found this effect was mostly driven by risk decreases for household and occupational activities, while the result for recreational activity alone was null (68). A 2007 Polish study, using the same questionnaire and similar methods to the Alberta case-control study, found an OR of 0.31 (95% CI: 0.21-0.70) among post-menopausal women for the highest vs. lowest MET-hrs/week tertile (all intensities combined) of lifetime physical activity from all three domains (69). When domains were analysed separately, similar ORs were observed for both recreational and household activity and no effect was observed for occupational activity, unlike the Alberta study (69). In both studies, odds ratios were null or non-significant among pre-menopausal women, except for an OR of 0.21 (95% CI: 0.06-0.68) for the highest vs. lowest tertile of lifetime household activity among pre-menopausal women in the Polish study (68,69).

Another Polish case-control study in 2008 found statistically significant protective ORs of 0.60 (95% CI: 0.42-0.87) for heavy occupational work, 0.81 (95% CI: 0.68-0.97) for outdoor activity, and 0.74 (95% CI: 0.62-0.89) for recreational MVPA (defined as MET≥4.5) for the highest vs. lowest lifetime hours/week activity tertile (71). Inconsistent with the two previous studies, no effect was observed for household activity (71). Also inconsistent with the above studies, a German case-control study of pre-menopausal women found increased breast cancer risk for the highest vs. lowest MET-hrs/week (all intensities combined) quartile of lifetime household activity (OR=1.48; 95% CI: 0.98-2.23) and no effect for lifetime sport or occupational activity

(72). Cycling was associated with reduced breast cancer risk (OR=0.66; 95% CI: 0.45-0.97 for the highest vs. lowest quartile) in an exposure-response fashion (p=0.03) (72).

The 2003 San Francisco Bay Area Breast Cancer Study found no effect for recreational activity, walking and bicycling, strenuous household activity, strenuous outdoor chores, moderate or strenuous jobs, or total sum of activity when analysed as hours/week for either pre- or post-menopausal women (52). When MET-hrs were applied to total activity, the highest vs. lowest tertile of moderate activity (3.0-5.9 METs) in all domains combined had an OR of 0.67 (95% CI: 0.46-0.96) among pre-menopausal women and 0.74 (95% CI: 0.59-0.94) among post-menopausal women (52). Separate activity domains were not analysed stratified by intensity.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the highest vs. lowest MET-hrs/week quartile (all intensities combined) of household activity was associated with reduced breast cancer risk among pre- and post-menopausal women (respective ORs = 0.71; 95% CI: 0.55-0.90 and 0.81; 95% CI: 0.70-0.93) in exposure-response fashions (respective p_{trend} values = 0.003 and 0.001) (70). Lifetime recreational and occupational physical activities were not associated with breast cancer risk (70). This cohort only examined physical activity in the past year, and thus may have missed the relevant physical activity exposure time period, which is likely earlier than one year prior to breast cancer diagnosis.

Thus, results from previous studies examining leisure-time, household, and occupational activities independent from one another are inconsistent. Results are generally protective, but no clear pattern of risk reductions by domain is evident from these results. None of these six studies adequately stratified physical activity by intensity to examine MVPA alone for each domain. Because the protective effects of physical activity appear strongest in the moderate-to-vigourous intensity range, examination of MVPA alone may be required to observe an effect.

2.6.4 Lifetime Period(s) of Physical Activity Exposure

In the context of physical activity and breast cancer, the "biologically effective age period" is the period of time in life where performance of physical activity is associated with the lowest risk for breast cancer. Multiple age periods may exist, as the etiology and latency periods for breast cancer are not fully known. For example, physical activity could conceivably exert anti-carcinogenic effects during adolescence and menopause, as both age periods are associated with hormonal events that increase risk for breast cancer. Measurement of age periods of exposure along the life course is thus essential for accurate physical activity exposure assessment to detect real time-sensitive associations, if they exist (73). Research that does not take age periods of physical activity exposure into account may be susceptible to non-differential misclassification of physical activity exposure.

Four of the studies that have investigated the simultaneous independent effects of leisure-time, household, and occupational MVPA have used a life course approach examining various lifetime exposure periods and/or average lifetime activity, and results are inconsistent (68,69,71,72). The Alberta case-control study examined total activity (sum of leisure-time, household, and occupational) stratified by age periods 0-17, 18-24, 25-44, 45-64, and 65-85 years, finding ORs of 0.73 (95% 0.54-0.98) for ages 0-17 and 0.72 (95% CI: 0.54-0.97) for ages 45-64 for the highest vs. lowest MET-hrs/week quartile of total activity among post-menopausal women (68). Effect estimates for other age periods were non-statistically significant. The 2007 Polish study examined recreational activity for the age periods of 14-20, 21-34, 35-50, and >50 years, finding ORs of 0.37 (95% CI: 0.23-0.60; p-trend<0.001) for ages 14-20 and 0.58 (95% CI: 0.27-1.27; p-trend=0.01) for ages >50 years for the highest vs. lowest MET-hrs/week tertile (69).

The 2008 Polish study examined age periods of 20-24, 25-29, 30-34, 35-39, 40-49, 50-59, and 60-69, and stratified by domain in addition to examining total activity for each age period (71). No distinctive pattern in ORs was discernible for any domain across age periods, although ORs were all in the protective direction (except those for occupational activity, which were slightly above 1.0) ranging between 0.67 and 0.99 and most were non- or borderline statistically significant (71). The strongest ORs were for the highest vs. lowest MET-hrs/week quartiles of household and recreational activity performed during ages 60-69 (OR=0.67; 95% CI: 0.47-0.94 for both domains) (71). The German study examined total activity (sum of walking, cycling, sports, household, and occupational) for age periods of 12-19 and 20-30 among pre-menopausal women only, finding ORs of 0.73 (95% CI: 0.50-1.07) for ages 12-17 and 0.96 (95% CI: 0.67-1.39) for ages 20-30 for the highest vs. lowest quartile of MET-hrs/week of total activity (72).

In these four studies, physical activity performed during adolescence and beyond age 50 appears to have stronger effects on breast cancer risk than activity performed at other age periods. Only one of these studies examined physical activity from different domains by lifetime period, and none examined the specific effects of MVPA. Further evidence to confirm the pattern emerging from these studies and to clarify specific aspects of physical activity domain and intensity by lifetime period would add to current knowledge.

2.6.5 Effect Modification by Menopausal Status

A systematic review conducted in 2007 on physical activity and breast cancer risk of 19 cohort and 29 case-control studies observed risk reductions ranging between 20 and 80% among post-menopausal women (51). These estimates were decreased to between 15 and 20% when pre-menopausal women were included, indicating a weaker effect of physical activity among this group (51). The 2011 narrative review found average risk reductions of 27% among

pre- and of 31% among post-menopausal women (4). These estimates are more similar than those found in the 2007 review and are based off of a larger number of studies.

The Alberta case-control study did not perform a formal test for significance of interaction by menopausal status, but found total lifetime physical activity to reduce breast cancer risk by 30% among post-menopausal women, with a null effect (OR=1.07) among pre-menopausal women (68). The 2007 Polish case-control study also did not test for significance of interaction, but found statistically significant risk reductions for different domains and age periods among post-menopausal women, with non-significant effects among pre-menopausal women (69). The San Francisco Bay Area Breast Cancer Study did not test for significance of interaction, but found slightly stronger ORs for pre- than for post-menopausal women (52). The 2008 Polish case-control study and a study among Asian-American women in Los Angeles tested for homogeneity of ORs between menopausal groups, finding no interaction (71,74).

Conflicting evidence from previous studies on presence of interaction by menopausal status may be in part due to heterogenous measures of physical activity. Further, since breast cancer is less common among pre-menopausal than post-menopausal women, studies including both menopausal groups tend to have a smaller number of pre-menopausal women. If the true difference in risk reduction between menopausal groups is small, then some studies may lack statistical power to detect differences in effect estimates between menopausal groups.

Despite conflicting evidence, menopausal status is accepted to modify the relationship between physical activity based on general trends of stronger risk reductions among post-menopausal women and plausibility of differences in biologic effects of physical activity between menopausal groups (see section 2.6.6) (12,75). However, whether or not energy expenditure dose, biologically effective age periods, and independent effects of different

activity domains differ between menopausal groups with respect to physical activity and breast cancer risk reduction is unknown.

2.6.6 Potential Biologic Anti-Carcinogenic Mechanisms of Physical Activity

The exact biologic mechanism(s) through which MVPA reduces breast cancer risk are unknown. However, a broad spectrum of interrelated mechanisms has been postulated, many of which reach an endpoint of lowered bodily estrogen levels. These proposed mechanisms include hormonal, metabolic, insulin-related, and inflammatory pathways (51,76).

One major possible pathway for post-menopausal women involves the main source of systemic estrogen post-menopause: through the conversion of androgens to estrogens by aromatase enzymes in adipose tissue (77). MVPA performed for 45 minutes on 5 days of the week for one year has been shown to significantly reduce adiposity, plasma estradiol, and free estradiol among post-menopausal women in the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) randomized controlled trial (55,56). Percent body fat and total body fat were found to mediate estradiol reduction in this trial (78). Another randomized trial among overweight and obese post-menopausal women using similar methods had similar results, except plasma estrone was significantly reduced in addition to estradiol (79). Thus, MVPA carried out by post-menopausal women may reduce risk through reduction of adiposity and levels of aromatase enzymes, and in turn, systemic estrogen levels (Figure 2.1).

MVPA delays menarche, shortens luteal phase length, and influences irregularity of the menstrual cycle, causing amenorrhea at the most extreme, all of which reduce lifetime estrogen exposure (80). These direct impacts on the ovaries and menstrual cycle are thought to be the primary estrogen-related anti-carcinogenic pathway of MVPA among pre-menopausal women

(Figure 2.1). These effects may reduce breast cancer risk later in life, but do not occur when MVPA is performed by post-menopausal women, as they no longer menstruate (80).

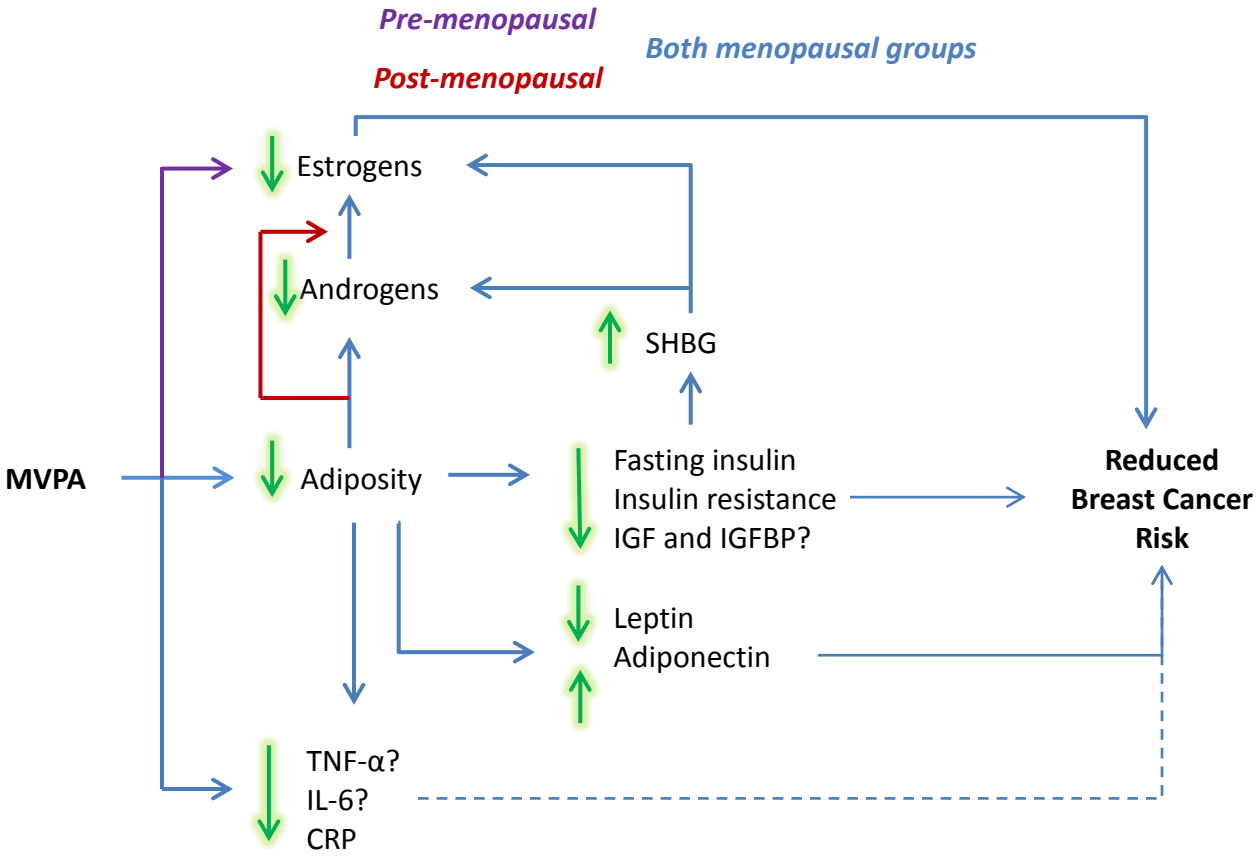
The ALPHA trial found reduced levels of fasting serum leptin, adiponectin (adipokines related to obesity and insulin resistance), insulin, and indicators of insulin resistance among the intervention arm (58). Circulating leptin levels correlate positively with body mass index and leptin is implicated in breast tumour proliferation, anti-apoptosis, and angiogenesis (81-83). Adiponectin has anti-inflammatory and anti-diabetic properties, and is negatively correlated with body mass index (81). Adiponectin has anti-proliferative effects on breast cancer cells, and the hypoadiponectinemia associated with obesity may inhibit these effects (81).

Reductions in body fat and fasting insulin level mediated an increase in circulating sex hormone binding globulin (SHBG) in the ALPHA trial (78). SHBG decreases the bioavailability of estradiol and testosterone by binding these hormones in the blood (76). Reduced fasting insulin also reduces systemic levels of insulin-like growth factor 1 (IGF-1) and increases levels of IGF binding proteins (IGFBP), thought to have apoptotic and anti-mitogenic effects on normal and metastatic breast tissue (51). However, both the ALPHA trial and the similar trial of overweight and obese post-menopausal women found no evidence for effect on IGF, IGFBP-3, or the ratio of the two, with exercise intervention (58,84).

Obesity results in a chronic state of low-grade inflammation characterized by elevated levels of the inflammatory markers: tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) (85). Chronic MVPA exerts anti-inflammatory effects by causing fat loss and preventing fat gain, and through direct effects on inflammatory and anti-inflammatory markers (85). However, epidemiologic evidence for the effects of TNF-α, IL-6, and CRP on breast cancer risk is scarce (4). In the ALPHA trial, MVPA intervention had no effect on circulating TNF-α

or IL-6, while a fat-loss-mediated CRP decrease was observed, although this effect was attenuated after adjustment for dietary fibre intake (57). No other randomized trials evaluating the effects of exercise on risk of developing breast cancer have examined insulin-related or inflammatory effects of MVPA, and further work is needed to corroborate results of the ALPHA trial.

Figure 2.1 Potential biologic anti-breast carcinogenic pathways of MVPA (adapted from Lynch *et al* and Neilson *et al* (4,76).



Blue, purple, and red arrows indicate pathways and green arrows indicate effects. TNF-α = tumour necrosis factor-alpha; IL-6 = interleukin-6; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein

In summary, potential anti-breast carcinogenic effects of MVPA involve interrelated hormonal, metabolic, insulin-related, and inflammatory pathways, which could act together in concert to reduce breast cancer risk (Figure 2.1). Whether these biologic effects extend to light intensity activities is unknown; it may be that MVPA is more efficacious than light intensity activity in producing these biologic effects.

Identification of age periods along the life course where physical activity is associated with reduced breast cancer risk may help elucidate these pathways. For instance, the biologically relevant time period for the aromatase reduction pathway is post-menopause, while the time window for the insulin-related pathway is less clear. Determination of biologically relevant age periods is therefore of importance for elucidation of the biologic mechanisms through which physical activity acts to reduce breast cancer risk, particularly when examining the two distinct lifetime periods of pre- and post-menopause.

2.6.7 Physical Activity and ER/PR & ER/PR/HER2-defined Tumour Subtypes

A 2008 review found five studies on the relationship between physical activity and ER/PR-defined breast cancers (51). The average effect estimate observed for ER-/PR- tumours was 0.61 among women with the highest vs. lowest activity level, stronger than the average effect estimate of 0.86 associated with ER+/PR+ tumours (51). Since then, four prospective and three case-control studies on physical activity and ER/PR-defined breast cancer risk have been conducted, with inconsistent results for heterogeneity in risk by tumour subtype (54,86-91). These studies used varied methods of assessing activity domain, intensity, and timing in life, which may in part be responsible for heterogeneity in results.

Three studies have examined physical activity in relation to risk for ER/PR/HER2-defined breast tumour subtype, albeit in a limited manners (32,37,92). The first, a case-control study of

women age 20-54, dichotomized cases and controls into two exposure groups based on median level of physical activity one year prior to interview. Protective ORs were observed for triple negative (0.73; 95% CI: 0.55-0.98), ER-/PR-/HER2+ (0.53; 95% CI: 0.31-0.92), ER+/PR+/HER2- (0.57; 95% CI: 0.45-0.71), and ER+/PR+/HER2+ (0.89; 95% CI: 0.53-1.50) tumours for women who met or exceeded the median physical activity level (32). Physical activity prior to the one-year exposure time window captured in this study was not considered, and the dichotomization of physical activity level caused loss of exposure information. Subsequently, non-differential misclassification of physical activity exposure may have occurred since physical activity domains captured were not indicated. Women older than age 54 were not studied.

The second study combined prospective observational and randomized data from the Women's Health Initiative study in the United States (37). This study of post-menopausal women found similar protective effects for recreational exercise on triple-negative and ER+ breast tumours, with respective hazard ratios of 0.77 (95% CI: 0.51-1.13) and 0.85 (95% CI: 0.74-0.98) among women in the highest physical exercise tertile vs. non-exercisers (37). PR and HER2 status were disregarded amongst the ER+ category defined by the investigators, and subsequently some tumour heterogeneity may have been present within this category. This study did not consider other sources of physical activity besides recreational exercise, which may have resulted in non-differential misclassification of physical activity exposure.

The third, a German case-control study of post-menopausal breast cancer, stratified ER+/PR+ breast cancer by HER2 status and found similar ORs for the highest quintile of leisure-time activity performed after age 50 for each subtype (0.76; 95% CI: 0.63-0.92 for ER+/PR+/HER- and 0.70; 95% CI: 0.46-1.05 for ER+/PR+/HER+) (92). This study did not examine physical activity outside of leisure-time and examined a relatively narrow time frame of activity.

Thus, while the three above studies, plus twelve examining ER/PR status, observed protective risk estimates for each tumour subtype, the scarcity of adequate epidemiological evidence at this point in time prevents definitive elucidation of any pattern in associations between physical activity and risk of breast tumour subtype. If physical activity reduces breast cancer risk through sex hormone-related mechanisms, then it may be most protective against hormone receptor-positive tumours. However, in most of the above studies protective effect estimates were the weakest for hormone receptor-positive tumours. The strongest significant association was with ER-/PR-/HER2+ tumours (32), which if confirmed may indicate an anti-carcinogenic mechanism for physical activity that is independent of hormone receptors and may be metabolic, insulin-related, or inflammatory in nature. Further high-quality evidence is needed to elucidate the true relationship between physical activity and risk of breast tumour subtypes.

2.7 Potential Confounders

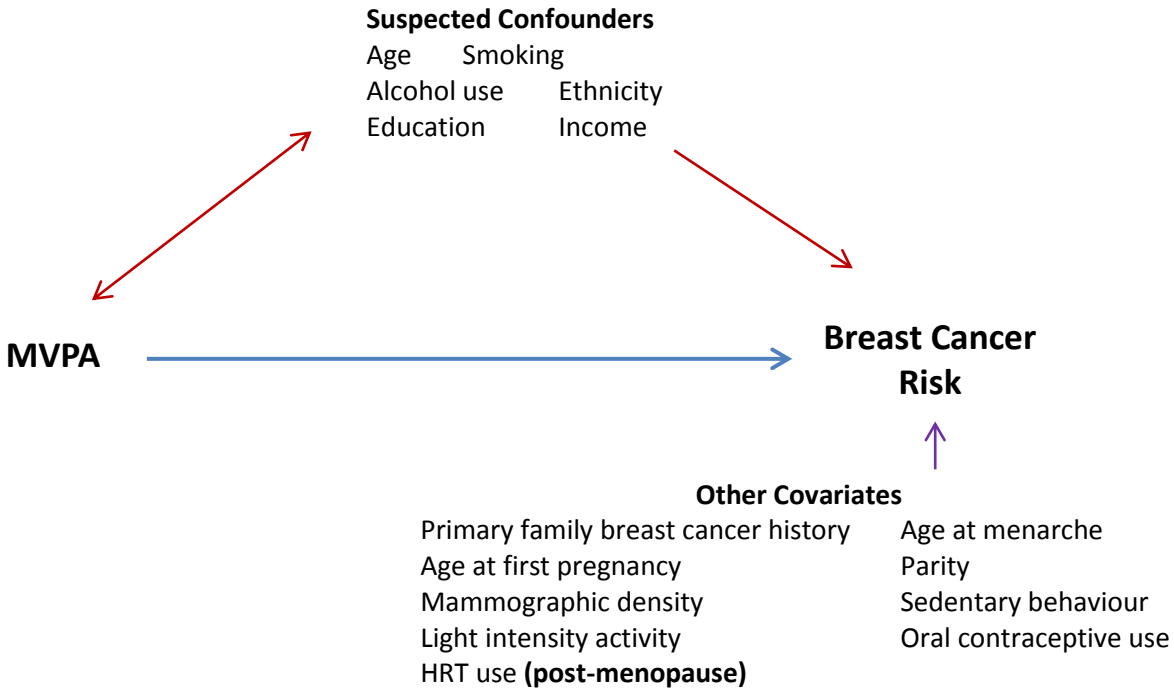
Extraneous factors related to either or both of MVPA and breast cancer risk must be accounted for in analyses of the effects of MVPA on breast cancer risk. These factors, shown in Figure 2.2, include lifestyle and reproductive factors, and influences upon lifestyle and reproductive factors. In the figure, factors listed as “Suspected Confounders” are associated with either MVPA and/or breast cancer risk, or are plausibly associated with both. Factors listed as “Other Covariates” are other relevant breast cancer risk factors that are not associated or not expected to be associated with MVPA.

2.7.1 Suspected Confounders

Besides sex, age is the single most important risk factor for female breast cancer (3). Physical activity habits plausibly change over the life course, and physical activity reporting varies by age (48). Ethnicity, education, and income are suspected demographic confounders

(3,93). Obesity is associated with reduced pre-menopausal and increased post-menopausal breast cancer risk (3), although obesity may be on the causal pathway (51). Smoking, a fatty diet, and alcohol use are associated with breast cancer risk (3,94). The former two factors are related to physical activity (95), although dietary factors were found to not confound the association between MVPA and breast cancer risk in three studies similar to this thesis (52,68,69).

Figure 2.2 Conceptual framework of suspected confounders and other covariates associated with MVPA and breast cancer risk



2.7.2 Other Covariates

Primary family history, age at menarche, parity, and age at first pregnancy, shown in Figure 2.2, are well-known risk factors not expected to be associated with physical activity (3). Sedentary behaviour and light intensity physical activity are of unknown relation to breast cancer (9), and are not well correlated with MVPA (Pearson's *r* = -0.27 for sedentary and -0.02

for light intensity activity (96)). Mammographic density is a breast cancer risk factor (97), but is not associated with MVPA (98). Oral contraceptive and hormone therapy use are associated with breast cancer risk (3), but use is not expected to differ by MVPA participation level.

2.8 Rationale

MVPA is accepted to reduce risk of developing breast cancer among pre- and post-menopausal women (4,61). Although over 90 studies have been published on MVPA and breast cancer risk, methodological disparities and inaccurate physical activity measurements have led to inconsistent risk estimates (4,9,75). Few studies have examined simultaneous independent effects of leisure-time, household, and occupational MVPA across the life course, and with inconsistent results (52,68,69). Most studies have not accounted for MVPA from different domains across the life course, and may be subject to misclassification of MVPA exposure and uncontrolled confounding if MVPA in different domains and age periods are related. Whether the anti-breast carcinogenic effects of MVPA are heterogeneous by ER/PR and ER/PR/HER2 tumour status is unknown. Finally, whether all of these aspects differ by menopausal status remains unknown. Elucidation of the relative importance of MVPA derived from different activity settings along the life course and specific effects on breast tumour subtypes will allow for development of specific policies targeting physical activity for breast cancer prevention among pre- and post-menopausal women. This research will examine effects of leisure-time, household, and occupational MVPA independent of one another simultaneously across the life course and during four age periods of exposure on overall breast cancer risk and risk of ER/PR-defined and ER/PR/HER2-defined breast tumour subtypes among pre- and post-menopausal women. Knowledge generated from this research will have potential for use in health policy targeting physical activity for breast cancer prevention among Canadian women.

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Chapter 3

Methods

3.1 Objectives

1. To describe lifetime MVPA energy expenditure cumulatively and over four age periods of exposure for pre- and post-menopausal cases and controls;
2. To determine the relationship between lifetime MVPA energy expenditure cumulatively and over four age periods of exposure and breast cancer risk separately within pre- and post-menopausal women; and,
3. To determine the relationship between lifetime MVPA energy expenditure cumulatively and during four age periods of exposure and risk of ER+ and/or PR+ and ER-/PR- breast tumours, and in an exploratory analysis, ER+ and/or PR+/HER2+, ER+ and/or PR+/HER2-, ER-/PR-/HER2+, and ER-/PR-/HER2- breast tumours, separately within pre- and post-menopausal women.

3.2 Study Population

A CIHR/CBCRA-funded case-control study of the Molecular Epidemiology of Breast Cancer (MEBC) was conducted in Vancouver, BC among women 20 to 80 years of age with no previous cancer history (except non-melanoma skin cancer). Eligible incident *in situ* or invasive breast cancer cases diagnosed between 2006 and 2010 and residing in Vancouver, Richmond, Burnaby and New Westminster were identified from the BC Cancer Registry. Over the same time period, controls residing in the same geographic area were randomly selected from cancer-free

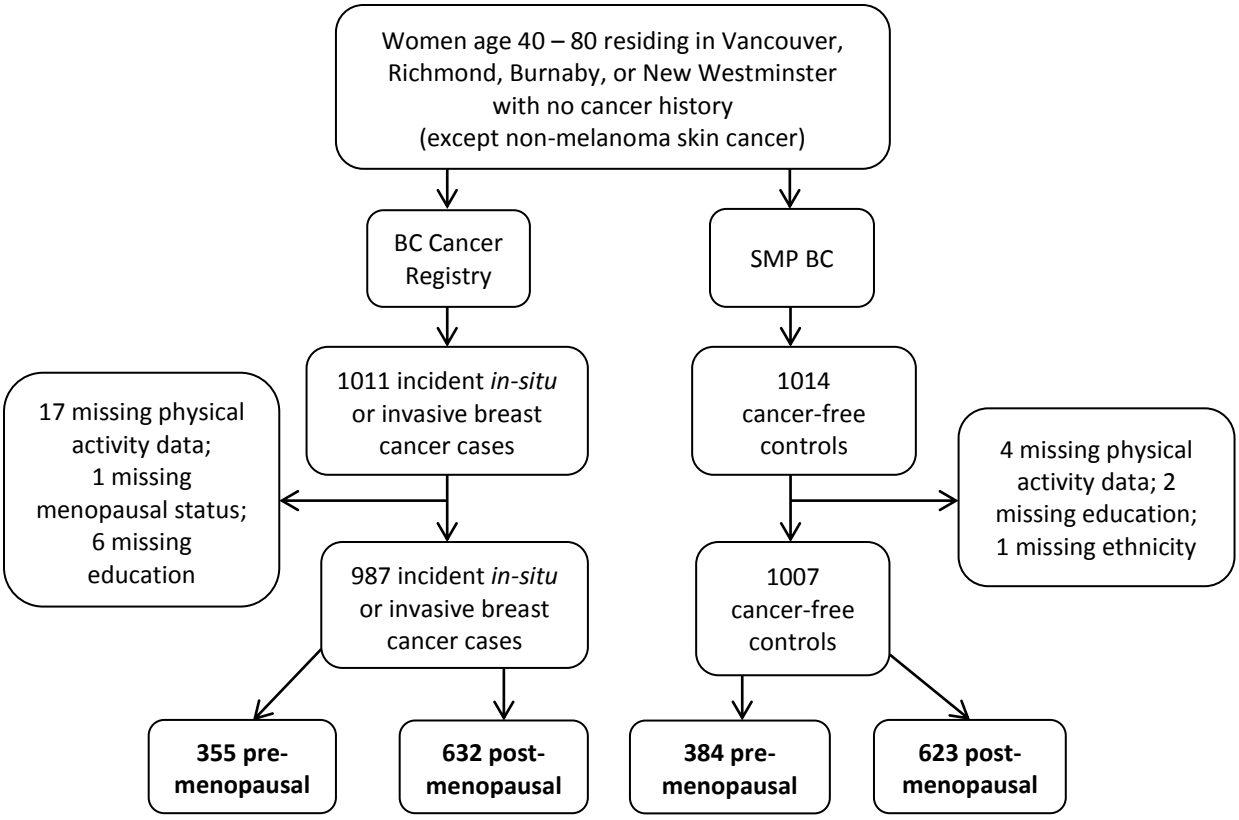
women enrolled in the Screening Mammography Program of BC (SMP BC) who had previously consented to participate in research studies at their last mammographic screening visit.

Potential cases and controls were mailed a study package, including a letter describing the study, a consent form, and study questionnaire. A total of 1,062 cases and 1,015 controls were recruited with written informed consent, with response rates of 54% for cases and 57% for controls. However, since the minimum age for enrolment in the SMP BC is 40 and subsequently no controls were under age 40, all cases under age 40 were excluded. Following this exclusion, 1,011 incident breast cancer cases and 1,014 controls remained. Controls were frequency matched to cases within five year age groups. All participants completed a detailed questionnaire and most provided a blood sample and medical records. Answers were collected through telephone interview by a trained interviewer. Participants who did not speak English were provided study materials in Chinese and Punjabi, as needed. A total of 987 cases and 1,007 controls had complete physical activity and covariate data and were included in this analysis (Figure 3.1).

3.2.1 Classification of Menopausal Status

Women were classified as post-menopausal if they reported: natural cessation of menstrual periods for at least one year; natural cessation of menstrual periods and were over 50 years of age, if time since last period was missing; or, if they were over age 55 and periods had stopped due to chemotherapy or other reasons, similar to Friedenreich *et al* (1). Of the total sample, 739 women were classified as pre-menopausal (355 cases; 384 controls) and 1255 were classified as post-menopausal (632 cases; 623 controls).

Figure 3.1 MEBC Study Recruitment Flow



3.3 Physical Activity Exposure Assessment

Lifetime leisure-time, household, and occupational physical activity information was collected using a self-report questionnaire adapted with permission from the Total Lifetime Physical Activity Questionnaire developed by Friedenreich *et al* (2) (Appendix B). Participants recorded the type, duration, frequency, and intensity (light, moderate, or vigourous) for regularly-performed household activities (at least 2 hours per week per year or 7 hours per week for 4 months for seasonal activities) and leisure-time activities (at least 32 hours total per year, or 40 minutes per week per year, or 2 hours per week for 4 months for seasonal activities). Lifetime occupational data collected included job title, industry, hours worked per week, number of years worked, and physical intensity (sedentary, light, moderate, or vigourous).

Questionnaire data are expected to be reliable, with Pearson correlation coefficients of 0.72, 0.77, and 0.87 for test-retest reliability of lifetime leisure-time, household, and occupational activity, respectively, determined in a pilot test among a study population similar to ours (2).

Leisure-time and household physical activity data were cleaned according to a set of data cleaning rules adapted from the Global Physical Activity Questionnaire (GPAQ), a validated and reliable physical activity questionnaire developed by the World Health Organization (WHO) (3). In brief, all values of 15, 30, 45, or 60 in the "hours" column for a specific activity were moved to the "minutes" column and the "hours" column was set to zero; household activities reported as >16 hours in duration were truncated to 16 hours to allow for an assumed 8 hours of sleep per night; leisure-time activities reported as >6 hours in duration were truncated to 6 hours (all reported leisure-time activities lasting >6 hours were: hiking, skiing, sailing, expedition, bicycling, golf; any of which as a full-day activity reasonably lasts for 6 hours); any activities reported as >7 days per week, >4 weeks per month, or >12 months per year were truncated to 7, 4, or 12, respectively; and, any activity reported with incomplete or inconsistent values (e.g., 0 days but >0 values in the hours or minutes columns) was deleted.

3.3.1 Classification of MVPA Exposure Variables

Lifetime household, leisure-time, and occupational MVPA data were summarized using metabolic equivalent (MET) scores, which are defined as the ratio of the calculated metabolic rate for a specific activity compared to resting metabolic rate (4,5). MET scores were abstracted from The Compendium of Physical Activities, an encyclopedia-like publication intended to standardize use of MET scores in scientific research (4,5). Leisure-time activities were assigned MET scores individually and household activities were categorized into one of nine general categories. Occupations reported as "moderate intensity" were assigned a MET score of 3.0 and

those reported as “heavy intensity” were assigned a MET score of 6.0. See Appendix C for detailed MET scores for each physical activity domain.

Among post-menopausal women, mean MET-hours per week of household and leisure-time MVPA was calculated for each of four distinct age periods: childhood/early adolescence (ages 12-17), early adulthood (ages 18-34), middle adulthood (ages 35-49), and late adulthood (ages ≥50). Mean MET-hrs/week of occupational MVPA was calculated for ages 18-34, 35-49, and ≥50, which was calculated up to age 65 or current age, whichever came first. Weekly MET-hours of MVPA averaged across the entire lifetime was also calculated for each physical activity domain (age 12 to current age for household and recreational physical activity and age 18 to age 65 or current age for occupational physical activity). Thus, 14 MVPA exposure variables were created for post-menopausal women (five each for household and recreational MVPA and four for occupational MVPA).

Among pre-menopausal women, mean MET-hrs per week of household and recreational MVPA was calculated for the first three lifetime periods only, due to the small number of pre-menopausal women over age 50 in this study (n=180). Mean MET-hrs/week of occupational MVPA was calculated for ages 18-34 and 35-49. Weekly MET-hours of MVPA averaged across the entire lifetime was also calculated for each physical activity domain (age 12 to current age for household and recreational physical activity and age 18 to current age for occupational physical activity). Thus, 11 MVPA exposure variables were created for pre-menopausal women (four each for household and recreational MVPA and three for occupational MVPA).

The age periods examined in this analysis were selected to maintain consistency with the original Total Lifetime Physical Activity Questionnaire (2). For participants who had not lived through an entire period (and for the ≥50 period) a weighted average of MET-hrs/week for that

period was determined with the number of weeks contributed to that period as the denominator. See Appendix D for example calculations.

3.4 Breast Cancer Outcome Assessment

Diagnostic information on breast cancer cases including ER, PR, and HER2 status of tumours was obtained from the BC Cancer Registry and the Breast Cancer Outcomes Unit at the time of data collection. Breast cancer cases were identified using the WHO's ICD-0-3 classification system (6). Eligible cases had an ICD code of C50, indicating a primary breast neoplasm, and a behaviour code of 3, indicating malignancy of the neoplasm.

This information was used to classify breast tumour subtype for each breast cancer case first by ER and PR status as ER/PR+ and ER-/PR-. These two groups were further stratified by HER2 status to create four tumour groups: ER/PR+/HER2-; ER/PR+/HER2+; ER-/PR-/HER2+; or ER-/PR-/HER2-. ER and PR statuses were determined using immunohistochemistry (IHC), each classified into one of six categories: OZER = negative (0/3), OLOW = weakly positive (1/3), OMOD = moderately positive (2/3), OHIG = strongly positive (3/3), OXXX = receptors tested but not sufficient quantity for interpretation or borderline/equivocal and XXXX = not tested. Tumours were considered ER or PR positive if they were classified as OLOW, OMOD or OHIG.

HER2 status was determined using IHC, or, if IHC produced indeterminable results, using fluorescence *in situ* hybridization (FISH). Using IHC, tumours were classified into one of seven categories: 0 = negative, 1 = weak staining (+1), 2 = moderate staining (+2; equivocal, indeterminate), 3 = strong staining (+3), 4 = positive, not quantified, 8 = not done/not applicable, 9 = done, result unknown. Using FISH, tumours were classified into one of six categories: 33 = indeterminate result (ratio >4.0 and < 8.0), 44 = negative (ratio ≤ 4.0), 55 = positive (ratio ≥ 8.0), 66 = negative, ratio not given, 77 = positive, ratio not given, 88 = not

done/not applicable, 99 = done, result unknown. Tumours were considered HER2 positive if classified as 1, 3, or 4 with IHC, or, if classified as 55 or 77 using FISH.

3.5 Covariates

Suspected confounders of the relationship between MVPA and breast cancer risk and other relevant covariates that have been assessed using the study questionnaire (Appendix B) are: age (continuous), ethnicity (White, Chinese, or Other), education level (secondary school or less, college diploma or trade certificate, undergraduate degree, or graduate or professional degree), primary family history of breast cancer (yes or no), age at menarche (continuous), ever pregnant (yes or no) number of live births (0, 1-3, ≥4), age at first pregnancy (continuous, among parous women only), ever breastfeeding (yes or no), ever oral contraceptive use (yes or no), ever hormone replacement therapy use (yes or no), lifetime pack-years of cigarette smoking (continuous; measured as the number of cigarettes smoked per day multiplied by number of years smoking with one pack year equal to smoking 20 cigarettes per day for one year), and mean weekly alcohol consumption (continuous; measured for total lifetime and specific to each age period examined). These factors are all known or suspected breast cancer risk factors plausibly associated with MVPA, or strong breast cancer risk factors warranting confounder assessment (7,8).

Since obesity, which is typically assessed using the body mass index (BMI), is likely on the causal pathway between MVPA and breast cancer risk, it was not considered as a confounder. A high-fat diet is associated with breast cancer risk (8) and with physical activity (9), although three studies similar to ours have found dietary factors to not confound this relationship (1,10,11). Dietary fat intake was not assessed in the MEBC study. With respect to indicators of socioeconomic status, common convention is to use a single measure of income,

occupation, or education, as the three are correlated (12). In the MEBC study, data were most complete for education, as is typical (12), and subsequently this variable was used as an indicator of socioeconomic status.

3.6 Statistical Analysis

3.6.1 Descriptive Analysis

Descriptive statistics were generated to express key characteristics of pre- and post-menopausal participants, including MVPA exposure, breast cancer outcome, and covariates of interest. Continuous covariates were described by calculating the mean and standard deviation. Categorical covariates were described as proportions. Breast cancer case status was described as proportion of pre- and post-menopausal study participants. Within cases, breast tumour subtypes were described as proportions. Univariate statistics describing MVPA exposure variables are outlined in the following section.

3.6.2 Objective 1

Among pre-menopausal participants, mean MET-hrs/week for each of household and recreational MVPA and 95% confidence intervals (CI) around the means were calculated for four lifetime periods (ages 12-17, 18-34, 35-49, and total lifetime). Mean MET-hrs/week of occupational MVPA and associated 95% CIs were calculated for three lifetime periods (ages 18-34, 35-49, and total adult lifetime). Among post-menopausal participants, mean MET-hrs/week for each of household and recreational MVPA and associated 95% CIs were calculated for five lifetime periods (ages 12-17, 18-34, 35-49, ≥50, and total lifetime). Mean MET-hrs/week of occupational MVPA and associated 95% CIs were calculated for four lifetime periods (ages 18-34, 35-49, 50-65 or current age, and total adult lifetime). Within each menopausal group, mean MET-hrs/week of MVPA for each of the three physical activity domains within each lifetime

period were compared between cases and controls using the Wilcoxon rank-sum test, as the distributions of MET-hrs/week of MVPA were highly left-skewed for all MVPA exposure variables.

Each continuous MVPA exposure variable was transformed into a categorical variable, where cases and controls with non-zero values were split into tertiles of mean MET-hrs/week based on the distribution amongst controls. Cases and controls with a mean of 0 MET-hrs/week of MVPA comprised the fourth category (the reference category for multivariate logistic regression analysis) for each exposure variable.

3.6.3 Objective 2

The hypothesis for this objective is that the magnitude of protective odds ratios for MVPA and the age period(s) in life where MVPA is most strongly associated with reduced breast cancer risk will differ by menopausal states, which may indicate differing biologic mechanisms between pre- and post-menopausal women.

Unconditional logistic regression was used to determine the relationship between leisure-time, household, and occupational MVPA by age period and risk of breast cancer separately within pre- and post-menopausal cases and controls. Bivariate associations between breast cancer case-control status and each suspected confounder or other covariate was determined using the chi-square test or Cochran-Armitage trend test for categorical covariates, the independent t-test for continuous, normally distributed covariates, and the Wilcoxon rank-sum test for continuous, non-normally distributed covariates. Suspected confounders and other covariates associated with breast cancer status with $p \leq 0.20$ were included in initial logistic regression models, and, using a change-in-estimate approach, were retained in final models if deletion changed odds ratio estimates by 10% or more (13). Age, education, ethnicity, and

MVPA from all three domains were always included in modeling. To examine whether associations between age period-specific MVPA and breast cancer risk were independent of MVPA performed in other age periods, a second set of models was additionally adjusted for MVPA performed in the other age periods.

3.6.4 Objective 3

The hypotheses for this objective are that MVPA will not be equally associated with all breast tumour subtypes, and that these associations will differ by menopausal status. If these hypotheses are correct, then results may indicate existence of differing biologic mechanisms for the effects of physical activity on each tumour subtype and menopausal state.

Bivariate associations between breast cancer case-control status, with cases first stratified into ER/PR+ and ER-/PR- subtypes and next into ER/PR+/HER2-, ER/PR+/HER2+, ER-/PR-/HER2+, and ER-/PR-/HER2- subtypes, and each suspected confounder or other covariate was determined using the chi-square test for categorical covariates, one-way ANOVA for continuous, normally distributed covariates, and the Kruskal Wallis test for continuous, non-normally distributed covariates. Suspected confounders and other covariates were then compared bivariately within case ER/PR-defined tumour subtypes, using the chi-square test for categorical covariates, Student's t-test for continuous, normally distributed covariates, and Wilcoxon rank-sum test for continuous, non-normally distributed covariates. Next, suspected confounders and other covariates were compared bivariately within case ER/PR/HER2-defined tumour subtypes, using the chi-square test for categorical covariates, one-way ANOVA for continuous, normally distributed covariates, and the Kruskal Wallis test for continuous, non-normally distributed covariates.

Polytomous logistic regression was used to determine the relationship between leisure-time, household, and occupational MVPA by lifetime period and risk of ER/PR and ER/PR/HER2-defined breast tumours separately within pre- and post-menopausal cases and controls. Polytomous logistic regression is a non-standard form of logistic regression where the response variable has more than two levels (14,15). Polytomous regression can be used for ordinal or nominal response categories and the choice of reference response category is flexible. The breast tumour subgroups examined in this thesis were treated as nominal categories and the control group served as the reference. Two sets of polytomous logistic regression models were created: one with the case group stratified into ER/PR+ and ER-/PR- tumours, and one with the case group stratified into ER/PR+/HER2-, ER/PR+/HER2+, ER-/PR-/HER2+, and ER-/PR-/HER2- tumours. Use of polytomous logistic regression allowed creation of a single and thus more parsimonious model to examine risk of each breast tumour subtype in relation to MVPA from each domain in each time period (14,15).

Tertiles of non-zero values of mean MET-hrs/week of MVPA (based on distribution among controls) were compared to 0 MET-hrs/week of MVPA as the reference category. Potential confounders were included in initial models if they were associated with breast cancer (case vs. control) at $p \leq 0.20$, and retained in final models if their deletion changed OR estimates by ≥10% (13). Age, education, ethnicity, and MVPA from all three domains were always included in modeling. Confounding variables selected in objective 2 using unconditional logistic regression were applied to polytomous logistic regression models.

Case-case polytomous logistic regression analyses were performed to determine heterogeneity of ORs associated with MVPA between tumour subtypes, generating p-values for tumour heterogeneity (p_{TH}). These models were controlled for the same confounders as the

case-control polytomous logistic regression models. For ER/PR-defined subtypes, ER/PR+ tumours served as the reference and for ER/PR/HER2-defined subtypes, ER/PR+/HER2- tumours served as the reference.

3.6.5 Minimum Detectable Effects

The primary objective of this research (objective 2) is to determine the relationship between MVPA energy expenditure performed during four time periods of exposure and cumulatively across the lifetime among pre- and post-menopausal women. Among pre-menopausal women in this study population, 355 are cases and 384 are controls. Among post-menopausal women, 632 are cases and 623 are controls. Among pre-menopausal women, assuming that MVPA exposure is distributed evenly amongst controls with 355 cases, an α-level of 0.05 and statistical power of 80%, the minimum detectable odds ratios are 0.60 and 1.57, when comparing the highest to the lowest MET-hrs/week of MVPA categories. Among post-menopausal women with 632 cases, an alpha-level of 0.05 and statistical power of 80% the minimum detectable odds ratios are 0.68 and 1.42.

Odds ratios of 0.60 and 0.68 are within the range of previously observed protective effect estimates for total lifetime physical activity and breast cancer risk. Of the studies most similar to this thesis, Kruk observed odds ratios of 0.44 and 0.31 for the highest tertiles of total lifetime MVPA for pre- and post-menopausal women, respectively (11). Peplonska et al. observed odds ratios of 0.74 and 0.60 for total lifetime recreational and occupational MVPA, respectively (16). Friedenreich et al. observed odds ratios of 1.07 and 0.70 for total lifetime physical activity for pre- and post-menopausal women, respectively, although these estimates included light activity, which may have less effect on breast cancer risk than MVPA (1,17).

3.6.6 Sensitivity Analysis

Since cases were recruited from a population-based registry and controls were recruited from a mammographic screening program, sensitivity analyses excluding cases who reported never having a mammogram or having their first mammogram <1 year prior to breast cancer diagnosis (n=173) were performed. All statistical analyses in this thesis were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

3.7 Ethical Considerations

Ethical approval for MEBC study was received from the University of British Columbia/BC Cancer Agency Research Ethics Board and the Queen's University Health Sciences Research Ethics Board. The candidate received expedited ethical approval specific to this thesis from the Queen's University Health Sciences Research Ethics Board (Appendix A). All paper questionnaires and consent forms for the MEBC study were stored in a secure, locked office at the BC Cancer Agency, and all electronic data were stored anonymized in a password-encrypted database on secure computers at the BC Cancer Agency and Queen's Cancer Research Institute. All data were analyzed anonymously.

3.8 Student Contributions

Under the guidance of Drs. Kristan Aronson and Ian Janssen, the candidate was responsible for the scientific conception, statistical analysis, interpretation of results, and all writing for this thesis. With input from Dr. Janssen, the candidate was responsible for cleaning all physical activity data in the MEBC dataset and creating all physical activity exposure variables.

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Chapter 4

Leisure-time, Household, and Occupational Physical Activity across the Life Course and Risk of Pre- and Post-Menopausal Breast Cancer

4.1 Abstract

Background: Moderate-to-vigourous intensity physical activity (MVPA) is accepted to reduce breast cancer risk, although previous studies have rarely examined activity performed outside of leisure-time using a life course approach while accounting for effect modification by menopausal status. We aimed to determine the independent effects of leisure-time, household, and occupational MVPA by age period across the life course on pre- and post-menopausal breast cancer risk.

Methods: A case-control study of 987 incident breast cancer cases and 1,007 cancer-free controls aged 40-80 was conducted from 2006-2010 in Vancouver, British Columbia. Lifetime leisure-time, household, and occupational MVPA were assessed by questionnaire and mean metabolic equivalent (MET)-hours per week of each were calculated for age periods 12-17, 18-34, 35-49, and ≥50 years and across the total lifetime. Odds ratios for pre- and post-menopausal breast cancer risk associated with each activity domain across age periods were estimated using unconditional logistic regression.

Results: Among post-menopausal women, >24.9 MET-hrs/week of average lifetime leisure-time MVPA (equivalent to running for 3 hours/week) and >79.5 MET-hrs/week of average lifetime household MVPA (equivalent to 21 hours/week of household work) reduced breast cancer risk by nearly 50%, compared to 0 MET-hrs/week of each. Leisure-time MVPA performed after age

35 was more strongly associated with reduced post-menopausal breast cancer risk than that performed in early life. Occupational MVPA performed during ages 18-34 was associated with a two-fold increase in pre-menopausal breast cancer risk.

Conclusions: This research supports the importance of leisure-time physical activity for reduction of post-menopausal breast cancer risk, especially when performed in later adulthood, and highlights the importance of active household work. Increased breast cancer risk associated with occupational MVPA may be attributable to occupational exposures not examined here. The amount of leisure-time MVPA required to reduce risk in our study was over three times higher than the current World Health Organization weekly physical activity recommendations for health, a disparity requiring further investigation.

4.2 Introduction

Moderate-to-vigorous intensity physical activity (MVPA) is one of the few modifiable risk factors for female breast cancer (1-4). Over 90 epidemiologic studies have examined this topic, with reviews finding risk reductions of 15-30% among active pre-menopausal women and 20-80% among active post-menopausal women (5-7). The range in risk reductions in previous research is likely due, in part, to heterogeneity in physical activity measurement and analysis (7). Physical activity is a complex construct. In addition to activity dose (e.g., energy expenditure), its measurement may include the activity domain (such as leisure-time activity, household work, and occupational work) and the time in life when the activity was accrued (7,8).

Most epidemiologic research on MVPA and breast cancer has focused on the leisure-time, recreational, and/or sport activity domain (7), although women perform MVPA in all domains of life. Canadian women spend a large proportion of their waking hours engaged in household work (4.4 hours/day on average) and occupational work (3.4 hours/day on average)

(9). By contrast, women spend 0.75 hours/day on average in leisure-time activities (9). The simultaneous effects of leisure-time, household, and occupational MVPA independent of one another on breast cancer risk have rarely been investigated (10-15). Generally, these studies show protective effects of varying magnitudes, although effect estimates are inconsistent across domains. Understanding of the relative importance of activity in each domain is important for development of policy targeting physical activity for breast cancer prevention.

Although 60% of etiology remains unknown, breast cancer in part results from accumulated and interactive hormonal exposures, the importance of which may vary at different times in life (16-18). MVPA, thought to primarily affect breast cancer risk through hormonal mechanisms (19,20), may exert anti-carcinogenic effects during hormonally critical age periods of life, such as menarche and menopause. MVPA across the total lifetime may also be beneficial, as metabolic and inflammatory mechanisms are also implicated in the etiology of breast cancer (21,22) and these pathways may be relevant at all ages. Measurement of MVPA performed at different age periods in life is thus essential to detect real time-sensitive associations, if they exist. Of the studies simultaneously examining leisure-time, household, and occupational MVPA independently, three have taken a life course approach examining different age periods and average total lifetime activity (10,12,14). No consensus is evident from these studies regarding the domain and timing in life most important for breast cancer risk reduction.

Menopausal status modifies the effect of MVPA on breast cancer risk, where observed effects tend to be stronger among post-menopausal women than among pre-menopausal women (23). MVPA is thought to impact sex hormone production directly through the ovaries among pre-menopausal women, and indirectly by reducing adiposity among post-menopausal women (2). Postulated metabolic and/or inflammatory mechanisms may affect both groups in

the same way (20). Two studies of leisure-time, household, and occupational MVPA across the life course (10,12) and one of average lifetime MVPA in each domain have stratified by menopausal status (11), with inconsistent results. If MVPA effects differ by domain and timing in life between menopausal groups, this finding would support differing biologic mechanisms of MVPA between these two groups. We sought to determine the independent associations between leisure-time, household, and occupational MVPA performed over the lifetime and during four age periods of exposure, and breast cancer risk among pre- and post-menopausal women.

4.3 Methods

4.3.1 Study Population

A case-control study ("Molecular Epidemiology of Breast Cancer" (MEBC)) was conducted among women ages 40-80 with no previous cancer history (except non-melanoma skin cancer). Eligible incident *in situ* and invasive breast cancer cases residing in Vancouver, Richmond, Burnaby, and New Westminster in British Columbia (BC) were identified from the BC Cancer Registry between 2006 and 2010. Pathology information for breast cancer cases was obtained from the BC Cancer Registry and the BC Breast Cancer Outcomes Unit. Controls recruited over the same time period were randomly selected cancer-free women enrolled in the Screening Mammography Program of BC who had consented to participate in research studies at their last mammographic screening visit and resided in the same geographic area as cases. Controls were frequency-matched to cases within five-year age groups.

Potential cases and controls were mailed a study package including a consent form and study questionnaire. All participants completed a detailed questionnaire and most provided a blood sample and consent to access medical records. Answers were collected through

telephone interview by a trained interviewer. Participants who did not speak English were provided study materials in Chinese, and Punjabi, as needed. In total, 1,011 incident breast cancer cases and 1,014 cancer-free controls were recruited, with response rates of 54% for cases and 57% for controls. A total of 987 cases and 1007 controls had complete physical activity and covariate data and were included in this analysis. Ethics approval for this study was received from the University of British Columbia/BC Cancer Agency Research Ethics Board and Queen's University Health Sciences Research Ethics Board.

Using self-reported questionnaire information, women were classified as post-menopausal if they reported: natural cessation of menstrual periods for at least one year; natural cessation of menstrual periods and were over 50 years of age, if time since last period was missing; or, if they were over age 55 and periods had stopped due to chemotherapy or other reasons, similar to Friedenreich *et al* (10). Using these criteria, 739 women were classified as pre-menopausal (355 cases; 384 controls) and 1255 were classified as post-menopausal (632 cases; 623 controls).

4.3.2 Physical Activity Exposure Measurement

Lifetime leisure-time, household, and occupational physical activity information was collected using a self-report questionnaire adapted from the Total Lifetime Physical Activity Questionnaire (24). Participants recorded the type, duration, frequency, and intensity (light, moderate, or heavy) for regularly-performed household activities (at least 2 hours per week per year or 7 hours per week for 4 months for seasonal activities) and leisure-time activities (at least 32 hours total per year, or 40 minutes per week per year, or 2 hours per week for 4 months for seasonal activities). Occupational data collected included job title, industry, hours worked per week, number of years worked, and physical intensity (sedentary, light, moderate, or heavy).

Regarding questionnaire data, Pearson correlation coefficients of 0.72, 0.77, and 0.87 for test-retest reliability of lifetime leisure-time, household, and occupational activity, respectively, were reported among a similar study population (24).

Household, leisure-time, and occupational MVPA energy expenditure were summarized using metabolic equivalent (MET) scoring. MET scores, defined as the ratio of the calculated metabolic rate for a specific activity compared to resting metabolic rate, were abstracted from the Compendium of Physical Activities for each reported activity (25). MET scores for leisure-time activities were abstracted individually and household activities were categorized into one of nine general categories. Occupations reported as "moderate intensity" were assigned a MET score of 3.0 and those reported as "heavy intensity" were assigned a MET score of 6.0. Mean MET-hrs/week of each activity domain were calculated for the adolescent (12-17 years), early adult (18-34 years), middle adult (34-49 years), and late adult (≥50 years) age periods, with the exception of occupational activity for the adolescent period, to maintain consistency with analytic methods for the original Total Lifetime Physical Activity Questionnaire (24). Mean MET-hrs/week of MVPA for each age period and for the total lifetime were calculated by multiplying MET scores with frequency and duration data from the questionnaire and weighted according to the number of weeks lived during each age period, or from age 12 to current age (or age 65 for post-menopausal occupational MVPA) for lifetime MVPA.

4.3.3 Potential Confounders

Potential confounders were: age (continuous), ethnicity (White, Chinese, or Other), education level (secondary school or less, college diploma or trade certificate, undergraduate degree, or graduate or professional degree), primary family history of breast cancer (yes or no), age at menarche (continuous), ever pregnant (yes or no) number of live births (0, 1-3, ≥4), age at

first pregnancy (continuous, among parous women only), ever breastfeeding (yes or no), ever oral contraceptive use (yes or no), ever hormone replacement therapy use (yes or no), lifetime pack-years of cigarette smoking (continuous), and mean weekly alcohol consumption (continuous; measured for total lifetime and specific to each age period examined). These variables were collected by self-report in the study questionnaire, and are all known or suspected breast cancer risk factors plausibly associated with MVPA (16,26). Since body mass index (BMI) is likely on the causal pathway between MVPA and breast cancer risk, it was not considered as a confounder.

4.3.4 Statistical Analysis

Odds ratios (ORs) for the associations between leisure-time, household, and occupational MVPA across the total lifetime and during distinct time periods with breast cancer were calculated using unconditional logistic regression separately within pre- and post-menopausal women. Tertiles of non-zero values of mean MET-hrs/week of MVPA (based on distribution among controls) were compared to 0 MET-hrs/week of MVPA as the reference category. Potential confounders were included in initial models if they were associated with the outcome at $p \leq 0.20$, and retained in final models if their deletion changed OR estimates by ≥10% (27). Age, education, ethnicity, and MVPA were always included in the models. Ever use of oral contraceptives and number of live births additionally remained in final models for pre-menopausal women, and no additional confounders remained in final models for post-menopausal women.

To examine whether associations between age period-specific MVPA and breast cancer risk were independent of MVPA performed in other age periods, a second set of models was

additionally adjusted for MVPA performed in the other age periods. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

4.4 Results

4.4.1 Descriptive Characteristics

Among both pre- and post-menopausal women, controls were more likely to be of European ethnicity, had higher educational achievement, were more likely to have ever used oral contraceptives, and drank more alcohol per week on average than cases, while cases were more likely to have a primary family history of breast cancer (Table 4.1). Among pre-menopausal women, cases had more live births than controls. Among post-menopausal women, cases were more likely to be overweight or obese than controls. Cases and controls were similar on all other characteristics.

4.4.2 Leisure-time MVPA

As shown in Table 4.2, among post-menopausal women, the highest tertile of total lifetime leisure-time MVPA (>24.9 MET-hrs/week) was associated with significantly reduced breast cancer risk compared to no lifetime leisure-time MVPA (0 MET-hrs/week), with OR=0.52 (95% CI: 0.34-0.80; p_{trend}=0.0006). Lifetime leisure-time MVPA was not associated with breast cancer risk among pre-menopausal women. Table 4.3 shows associations between MVPA and breast cancer risk, stratified by age period. Leisure-time MVPA performed during ages 12-17 was not associated with pre-menopausal breast cancer risk, while leisure-time MVPA during ages 18-34 and 35-49 were of borderline statistical significance (p_{trend}=0.06 for both age periods). Among post-menopausal women, leisure-time MVPA performed during ages 35-49 (p_{trend}=0.0002) and ≥50 (p_{trend}=0.003) were more strongly associated with reduced breast cancer risk than leisure-time MVPA performed during ages 12-17 and 18-34 (p_{trend}=0.06 for both). When leisure-time

MVPA in each age period was examined independently by adjusting for leisure-time MVPA in other age periods, odds ratios were similar (results not shown).

4.4.3 Household MVPA

Among post-menopausal women, the highest tertile of total lifetime household MVPA (>79.5 MET-hrs/week) was associated with significantly reduced breast cancer risk compared to no lifetime household MVPA, with OR=0.55 (95% CI: 0.40-0.77; p_{trend}=0.001; Table 4.2). Among post-menopausal women, adulthood age period-specific odds ratios were similar to those for the total lifetime, while household MVPA during ages 12-17 was not associated with breast cancer risk (Table 4.3). Household MVPA across the total lifetime and at each age period was not associated with pre-menopausal breast cancer risk (Tables 4.2 and 4.3). When household MVPA in each age period was adjusted for household MVPA in other age periods, odds ratios were similar (results not shown).

4.4.4 Occupational MVPA

As shown in Table 4.2, among post-menopausal women, there was no association between lifetime occupational MVPA and breast cancer risk (p_{trend}=0.07). Among pre-menopausal women, the highest tertile of occupational MVPA (> 89.1 MET-hrs/week) was associated with increased breast cancer risk compared to no lifetime occupational MVPA (OR=1.57; 95% CI: 1.03-2.39; p_{trend}=0.01). When occupational MVPA during ages 18-34 and 35-49 were adjusted for each other, MVPA during ages 18-34 was associated with increased breast cancer risk (p_{trend}=0.008), while no effect was observed for ages 35-49 (p_{trend}=0.58; Table 4.3). Among post-menopausal women, adjustment of occupational MVPA in each age period for occupational MVPA in other age periods resulted in minimal changes to ORs (not shown).

4.4.5 Sensitivity Analysis

Because cases were population-based and controls were recruited from the BC provincial mammographic screening program, a sensitivity analysis excluding all cases who reported never having a mammogram or having their first mammogram less than one year prior to breast cancer diagnosis was performed (n=173 cases excluded). Results were nearly identical to the original analyses (not shown).

4.5 Discussion

This study considered the simultaneous effects of leisure-time, household, and occupational MVPA across the life course on breast cancer risk while accounting for effect modification by menopausal status. Both leisure-time and household MVPA were independently associated with decreased risk of post-menopausal breast cancer, with risk reductions of nearly 50% among women in the highest tertiles of lifetime activity in each domain. Associations with lifetime leisure-time and household MVPA were not statistically significant among pre-menopausal women.

Our findings are consistent with five similar studies of lifetime leisure-time, household, and occupational physical activity, although some other studies report stronger effects among pre-menopausal women (10-12,14,15). One similar study found a reduced risk associated with household MVPA, but not leisure-time MVPA (13). In our study, leisure-time MVPA performed during middle and late adulthood (ages 35-49 and ≥50) was more strongly associated with reduced post-menopausal breast cancer risk than leisure-time MVPA performed earlier in life (ages 12-17 and 18-34). This finding is consistent with results from two of the three studies most similar to ours, where the first, a 2001 Canadian case-control study, found strongest risk reductions for activity performed between ages 0-17 and 45-64 (10) and the second, a 2008 Polish case-control study, found strongest risk reductions for activity performed during ages 40-

49 and 50-59 (14). The third study found that leisure-time physical activity performed in adolescence is most important for risk reduction (12). Recall of MVPA performed during ages 35-49 and ≥50 may be better than of that performed during ages 12-17 and 18-34, although reliability statistics are similar across age periods with the questionnaire we used (24). Our finding may also represent the lifetime accumulation of protective hormonal, metabolic, and inflammatory effects of MVPA, since MVPA in early life was moderately positively correlated with activity later in life in this study.

In our study, reduction in post-menopausal breast cancer risk was observed at 24.9 MET-hrs/week of lifetime leisure-time MVPA, which is equivalent to running 3 hours per week or brisk walking for 7.5 hours per week. This weekly MVPA energy expenditure dose is over three times higher than the current World Health Organization physical activity recommendations, which state that 75 min/week of vigourous (e.g., running) or 150 min/week of moderate (e.g., brisk walking) physical activity are effective in reducing risk for several health outcomes, including breast cancer (3). Current physical activity guidelines recognize that it takes about twice as long to expend the same energy expenditure with moderate intensity activities than with vigourous intensity activities and focus on achieving a comparable energy expenditure dose with either intensity or an equivalent combination of the two. However, the specific effects of higher volume moderate intensity activity versus lower volume vigourous intensity activity on breast cancer risk remain to be elucidated.

Other results also indicate that the MVPA energy expenditure dose required to reduce breast cancer risk is higher than current physical activity recommendations. Two narrative reviews have concluded that 30-60 min/day (equal to 210-420 minutes/week) (28) and 4-7 hours/week (240-420 min/week) (29) of MVPA are required to reduce risk. In the U.S. NIH-AARP

Diet and Health Study, leisure-time MVPA was associated with a 16% reduction in breast cancer risk at >7 hrs/week (>420 min/week), with no effect at lower weekly doses (30). Confirmation of the weekly MVPA energy expenditure dose required to reduce breast cancer risk will be important for future physical activity recommendations for breast cancer prevention.

The stronger effects we observed among post-menopausal women compared to pre-menopausal women are consistent with findings from the 2001 Canadian and 2007 Polish case-control studies (10,12). The 2008 Polish study found no evidence of interaction by menopausal status (14). Among post-menopausal women, 45 min of MVPA 5 days per week has been shown in a randomized trial to reduce adiposity and circulating estrogen levels, and improve insulin sensitivity (19,21,22). Reduction in adiposity may at least partially mediate the effects of MVPA on sex hormones (31), an effect which may be confined to post-menopausal women as adipose tissue is the main source of systemic estrogen post-menopause (78). Hence, the effects of MVPA may be less efficacious on pre-menopausal women, as adipose tissue is less important for endogenous estrogen metabolism among this group (32). The relative contributions of adiposity-dependent and independent effects of MVPA on sex hormones to affect breast cancer risk remains uncertain among both menopausal groups.

After accounting for leisure-time and household MVPA, lifetime occupational MVPA was associated with increased breast cancer risk at >86.6 MET-hrs/week among pre-menopausal women and between 33.6 – 95.0 MET-hrs/week among post-menopausal women. These MET volumes are equivalent to working 29 hours per week and 11-32 hours per week, respectively, in a job involving brisk walking and light lifting. These findings are inconsistent with previous research indicating protective effects of occupational physical activity on breast cancer risk (7,10-12,33,34). Two previous studies have reported increases in breast cancer risk associated

with jobs involving moderate or heavy physical energy expenditure (35,36). The first, designed to address high cancer incidence in Cape Cod, Massachusetts, found a 70% increase in risk associated with spending 10+ years in a medium/heavy physical job (35). The second, using a National Cancer Institute job exposure matrix, found an increase in risk among post- but not pre-menopausal women, attributing it to industrial exposures encountered by these women who worked in factories during World War II (36). The effect modification by age period we observed among pre-menopausal women, whereby a doubling in risk was associated with occupational MVPA during ages 18-34 and no effect was observed for ages 35-49, is of particular interest for further analyses of occupational physical activity and other exposures.

Strengths of this study include its large sample size, separate examination of menopausal groups, and comprehensive lifetime physical activity exposure assessment. Specifically, we investigated leisure-time, household, and occupational MVPA independently by age period across the life course. Physical activity data were collected by self-report and although our questionnaire was reliable, some non-differential error in recall of physical activity may have occurred: this would cause our results to underestimate the true effects of MVPA on breast cancer risk. Reassuringly for our study, habitual and moderate and vigourous intensity activities are associated with better recall than sporadic and light intensity activities with the questionnaire we used (24). The physical activity questionnaire was part of a larger questionnaire, and recall bias with respect to physical activity is not expected to have occurred.

Since cases were population-based and controls were screening clinic-based, a concern may be that some cases may have never participated in routine mammographic screening, and thus would have been ineligible to become controls had they not developed breast cancer. However, in a sensitivity analysis excluding cases unlikely to have participated in routine

mammographic screening, our results were negligibly changed. Relatively low response rates for cases and controls have potential to introduce response bias into our results. However, because the response rate was similar between cases and controls and because we have no reason to expect that study response was related to physical activity, we expect effects on our results to be minimal.

This research supports the importance of MVPA performed during leisure-time particularly after age 35, and highlights the role of active household activities in reducing breast cancer risk among post-menopausal women. Effects appear less efficacious or obvious among pre-menopausal women. Moderate-to-vigorous occupational physical activity was associated with slightly increased breast cancer risk among both pre- and post-menopausal women, although these findings may be related instead to other occupational exposures not investigated here. The amount of leisure-time MVPA required to reduce post-menopausal breast cancer risk was over three times the weekly amount recommended by the WHO for breast cancer risk reduction, a disparity requiring further investigation.

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Table 4.1 Descriptive characteristics of study population

	Pre-menopausal Women (n=739)			Post-menopausal Women (n=1,255)		
	Cases (n=355) n (%)	Controls (n=384) n (%)	p-value	Cases (n=632) n (%)	Controls (n=623) n (%)	p-value
Age (mean±SD)	47.0±4.0	47.3±3.7	0.22[a]	62.6±8.2	62.8±8.0	0.62[a]
Education						
High School or less	78 (22)	60 (16)	**0.008**[c]	261 (41)	183 (29)	**<0.0001**[c]
College Degree/Certificate	111 (31)	115 (30)		177 (28)	180 (29)	
Bachelor's Degree	116 (33)	135 (35)		128 (20)	131 (21)	
Graduate/Professional Degree	50 (14)	74 (19)		66 (10)	129 (20)	
Ethnicity						
European	180 (51)	263 (68)	**<0.0001**[b]	396 (62)	493 (79)	**<0.0001**[b]
Chinese	105 (29)	57 (15)		131 (21)	55 (9)	
Other	70 (20)	64 (17)		105 (17)	75 (12)	
BMI at study entry						
Underweight (≤18.49)	12 (3)	12 (3)	0.25[c]	14 (2)	14 (2)	**0.0006**[c]
Normal (18.5 – 24.99)	223 (63)	236 (61)		294 (47)	342 (55)	
Overweight (25.00 – 29.99)	85 (24)	86 (23)		203 (32)	185 (30)	
Obese (≥30.00)	29 (8)	46 (12)		116 (18)	75 (12)	
Missing	6 (2)	4 (1)		6 (1)	7 (1)	
1° family hx of breast cancer						
Yes	61 (17)	48 (12)	0.07[b]	133 (21)	86 (14)	**0.0007**[b]
No	294 (83)	336 (88)		499 (79)	537 (86)	
Age at menarche (mean±SD)	12.7±1.4	12.8±1.5	0.50[a]	13.0±1.7	12.8±1.5	0.16[a]
Ever Oral Contraceptive Use						
Yes	191 (54)	277 (72)	**<0.0001**[b]	335 (53)	370 (59)	**0.02**[b]
No	164 (46)	107 (28)		297 (47)	253 (41)	
Ever pregnant						
Yes	285 (80)	277 (72)	**0.01**[b]	527 (84)	508 (82)	0.32[b]
No	70 (20)	107 (28)		105 (16)	115 (18)	
Age at 1st pregnancy (mean ±SD)	28.1±4.9	28.0±5.1	0.72[a]	26.1±4.9	26.2±4.4	0.94[a]
Number of live births						
0	107 (30)	147 (38)	**0.003**[b]	142 (22)	161 (26)	0.37[b]
1-3	244 (69)	223 (58)		439 (69)	415 (67)	
≥4	4 (1)	14 (4)		51 (8)	47 (8)	
Ever breastfeeding						
Yes	207 (58)	213 (55)	0.43[b]	354 (56)	359 (58)	0.56[b]
No	148 (42)	171 (45)		278 (44)	264 (42)	
Ever HRT Use ‡						
Yes	-	-	-	286 (45)	297 (48)	0.40[b]
No	-	-		344 (55)	325 (52)	
Lifetime smoking pack-years (mean±SD)	3.0±7.1	5.1±35.6	0.62[d]	6.8±13.9	6.9±23.0	0.81[d]
Alcoholic drinks/week (mean±SD)						
Lifetime	2.4±3.8	3.7±5.0	**<0.0001**[d]	2.7±5.7	3.3±4.6	**<0.0001**[d]
Adolescence (ages 12-17)	1.4±4.0	2.1±4.2	**<0.0001**[d]	0.8±3.4	1.2±3.5	**<0.0001**[d]
Early adulthood (ages 18-34)	2.6±4.6	4.2±7.1	**<0.0001**[d]	2.6±5.9	3.4±6.2	**<0.0001**[d]
Middle adulthood (ages 35-49)	2.5±4.1	3.7±5.1	**<0.0001**[d]	3.1±6.7	3.4±5.2	**<0.0001**[d]
Late adulthood (ages ≥50)	-	-	**-**	3.0±5.5	3.4±5.2	**<0.0001**[d]

[a] Independent samples t-test
[b] Chi-square test
[c] Cochran-Armitage trend test
[d] Wilcoxon rank-sum test
‡ Note: 3 participants missing

Table 4.2 Adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the association between lifetime MVPA and breast cancer risk among pre- and post-menopausal women

Pre-menopausal (355 cases; 384 controls)				Post-menopausal (632 cases; 623 controls)			
MVPA (mean MET-hrs/wk)	Cases (n %)	Controls (n %)	Multivariate-adjusted OR (95% CI)[a]	MVPA (mean MET-hrs/wk)	Cases (n %)	Controls (n %)	Multivariate-adjusted OR (95% CI)[b]
a) Leisure-time MVPA							
0 MET-hrs/wk	41 (12)	31 (8)	1.00 (reference)	0 MET-hrs/wk	99 (16)	67 (11)	1.00 (reference)
≤10.9	150 (42)	115 (30)	1.14 (0.65, 1.99)	≤8.5	242 (38)	183 (29)	0.98 (0.67, 1.44)
10.91 – 25.3	81 (23)	117 (30)	0.70 (0.39, 1.27)	8.51 – 24.9	185 (29)	182 (29)	0.90 (0.60, 1.34)
>25.3	83 (23)	121 (31)	0.80 (0.44, 1.47)	>24.9	105 (17)	191 (31)	**0.52 (0.34, 0.80)**
p trend			0.09				**0.0006**
b) Household MVPA							
0 MET-hrs/wk	129 (36)	134 (35)	1.00 (reference)	0 MET-hrs/wk	219 (35)	159 (25)	1.00 (reference)
≤13.2	63 (18)	82 (21)	1.02 (0.66, 1.59)	≤24.8	143 (23)	153 (25)	0.80 (0.57, 1.10)
13.21 – 62.0	83 (23)	83 (22)	1.10 (0.71, 1.69)	24.81 – 79.5	153 (24)	153 (25)	0.82 (0.59, 1.13)
>62.0	80 (23)	85 (22)	0.89 (0.57, 1.40)	>79.5	117 (19)	158 (25)	**0.55 (0.40, 0.77)**
p trend			0.73				**0.001**
c) Occupational MVPA							
0 MET-hrs/wk	119 (34)	161 (41)	1.00 (reference)	0 MET-hrs/wk	241 (38)	266 (43)	1.00 (reference)
≤26.0	61 (17)	73 (19)	1.31 (0.84, 2.03)	≤32.8	112 (18)	117 (19)	1.18 (0.85, 1.64)
26.01 – 89.1	88 (25)	74 (19)	**1.60 (1.06, 2.42)**	32.81 – 94.6	147 (23)	118 (19)	**1.48 (1.08, 2.03)**
>89.1	87 (25)	76 (20)	**1.57 (1.03, 2.39)**	>94.6	132 (21)	122 (20)	1.26 (0.91, 1.74)
p trend			**0.01**				0.07

[a] Adjusted for age, education, ethnicity, ever oral contraceptive use, number of live births, and other domains of lifetime MVPA in table.

[b] Adjusted for age, education, ethnicity, and other domains of lifetime MVPA in table.

Table 4.3 Adjusted ORs (95% CI) for the association between MVPA by age period and breast cancer risk among pre- and post-menopausal women

Pre-menopausal (355 cases; 384 controls)				Post-menopausal (632 cases; 623 controls)			
MVPA (mean MET-hrs/wk)	Cases (n %)	Controls (n %)	OR (95% CI) [a]	MVPA (mean MET-hrs/wk)	Cases (n %)	Controls (n %)	OR (95% CI) [b]
a) Leisure-time							
12 – 17 years							
0 MET-hrs/wk	102 (29)	100 (26)	1.00 (referent)	0 MET-hrs/wk	235 (37)	188 (30)	1.00 (referent)
≤12.1	81 (23)	93 (25)	0.97 (0.63, 1.49)	≤15.0	161 (25)	144 (23)	1.01 (0.74, 1.37)
12.11 – 33.0	90 (25)	94 (24)	1.36 (0.88, 2.11)	15.01 – 39.6	140 (22)	143 (23)	1.00 (0.73, 1.37)
>33.0	81 (23)	97 (25)	1.20 (0.77, 1.87)	>39.6	96 (15)	148 (24)	**0.68 (0.49, 0.96)**
p trend			0.23				0.06
18 – 34 years							
0 MET-hrs/wk	103 (29)	82 (21)	1.00 (referent)	0 MET-hrs/wk	241 (38)	201 (32)	1.00 (referent)
≤8.1	115 (32)	99 (26)	1.16 (0.76, 1.78)	≤7.0	181 (29)	139 (22)	1.27 (0.94, 1.72)
8.11 – 24.1	74 (21)	100 (26)	0.74 (0.47, 1.18)	7.01 – 22.0	125 (20)	139 (22)	1.01 (0.73, 1.40)
>24.1	63 (18)	103 (27)	0.73 (0.45, 1.19)	>22.0	85 (13)	144 (23)	0.70 (0.49, 1.00)
p trend			0.06				0.06
35 – 49 years							
0 MET-hrs/wk	121 (34)	94 (24)	1.00 (referent)	0 MET-hrs/wk	308 (49)	213 (34)	1.00 (referent)
≤10.3	106 (30)	95 (25)	1.07 (0.71, 1.62)	≤9.2	136 (21)	134 (21)	0.85 (0.62, 1.15)
10.31 – 28.9	71 (19)	96 (25)	0.80 (0.52, 1.25)	9.21 – 27.6	113 (18)	136 (22)	0.76 (0.55, 1.06)
>28.9	57 (16)	99 (26)	0.68 (0.42, 1.08)	>27.6	75 (12)	140 (22)	**0.49 (0.34, 0.70)**
p trend			0.06				**0.0002**
≥50 years							
-	-	-	-	0 MET-hrs/wk	242 (40)	174 (28)	1.00 (referent)
-	-	-	-	≤8.8	135 (22)	141 (23)	0.76 (0.55, 1.04)
-	-	-	-	8.81 – 26.2	145 (24)	142 (23)	0.91 (0.67, 1.24)
-	-	-	-	>26.2	81 (13)	147 (24)	**0.52 (0.37, 0.74)**
p trend			-				**0.003**
b) Household							
12 – 17 years							
0 MET-hrs/wk	305 (86)	320 (83)	1.00 (referent)	0 MET-hrs/wk	539 (85)	523 (84)	1.00 (referent)
≤8.0	16 (5)	21 (5.5)	0.94 (0.46, 1.91)	≤10.2	24 (4)	33 (5)	0.88 (0.50, 1.53)
8.01 – 44.3	22 (6)	21 (5.5)	1.37 (0.71, 2.63)	10.21 – 41.7	34 (5)	33 (5)	1.11 (0.67, 1.86)
>44.3	12 (3)	22 (6)	0.48 (0.23, 1.03)	>41.7	35 (6)	34 (6)	0.97 (0.59, 1.62)
p trend			0.33				0.98
18 – 34 years							
0 MET-hrs/wk	162 (46)	155 (40)	1.00 (referent)	0 MET-hrs/wk	266 (42)	192 (31)	1.00 (referent)
≤9.5	51 (15)	75 (20)	0.76 (0.48, 1.19)	≤29.9	116 (18)	142 (23)	**0.71 (0.51, 0.98)**
9.51 – 66.5	66 (18)	74 (19)	0.91 (0.59, 1.41)	29.91 – 99.7	114 (18)	142 (23)	**0.64 (0.46, 0.88)**
>66.5	76 (21)	80 (21)	0.76 (0.49, 1.18)	>99.7	136 (22)	147 (24)	**0.68 (0.50, 0.92)**
p trend			0.28				**0.006**
35 – 49 years							
0 MET-hrs/wk	160 (45)	161 (42)	1.00 (referent)	0 MET-hrs/wk	281 (45)	200 (32)	1.00 (referent)
≤16.3	61 (17)	73 (19)	0.98 (0.64, 1.50)	≤26.9	113 (18)	139 (22)	**0.67 (0.49, 0.93)**
16.31 – 103.6	64 (18)	74 (19)	0.94 (0.61, 1.44)	26.91 – 114.3	116 (16)	139 (22)	**0.62 (0.45, 0.86)**
>103.6	70 (20)	76 (20)	0.82 (0.52, 1.28)	>114.3	122 (21)	145 (23)	**0.65 (0.48, 0.89)**
p trend			0.40				**0.002**
≥50 years							
-	-	-	-	0 MET-hrs/wk	372 (62)	284 (47)	1.00 (referent)
-	-	-	-	≤8.1	66 (11)	104 (17)	**0.57 (0.40, 0.81)**
-	-	-	-	8.11 – 67.0	95 (16)	107 (18)	0.84 (0.60, 1.17)

-	-	-	-	>67.0	70 (12)	109 (18)	**0.52 (0.36, 0.74)**
p trend			-				**0.0007**
c) Occupational							
18-34 years [c]							
0 MET-hrs/wk	156 (44)	196 (51)	1.00 (referent)	0 MET-hrs/wk	333 (53)	333 (53)	1.00 (referent)
≤38.8	55 (15)	62 (16)	1.43 (0.91, 2.24)	≤49.4	95 (15)	92 (15)	1.20 (0.86, 1.69)
38.81 – 91.7	65 (18)	62 (16)	**1.71 (1.06, 2.79)**	49.4 – 105.0	101 (16)	100 (16)	1.18 (0.85, 1.64)
>91.7	79 (22)	64 (17)	**2.02 (1.18, 3.46)**	>105.0	103 (16)	98 (16)	1.03 (0.74, 1.44)
p trend			**0.008**				0.73
35-49 years [d]							
0 MET-hrs/wk	199 (56)	229 (60)	1.00 (referent)	0 MET-hrs/wk	336 (53)	368 (59)	1.00 (referent)
≤68.6	47 (13)	51 (13)	0.69 (0.42, 1.15)	≤66.4	82 (13)	85 (14)	1.03 (0.73, 1.47)
68.61 – 121.6	38 (11)	52 (14)	**0.53 (0.30, 0.91)**	66.41 – 122.4	105 (17)	84 (13)	**1.45 (1.03, 2.03)**
>121.6	71 (20)	52 (14)	0.89 (0.51, 1.55)	>122.4	109 (17)	86 (14)	1.28 (0.92, 1.80)
p trend			0.58				0.25
≥50 years							
-	-	-	-	0 MET-hrs/wk	356 (59)	389 (64)	1.00 (referent)
-	-	-	-	≤57.0	70 (12)	70 (12)	1.01 (0.69, 1.48)
-	-	-	-	57.01 – 97.9	68 (11)	71 (12)	1.08 (0.74, 1.59)
-	-	-	-	>97.9	109 (18)	74 (12)	**1.60 (1.13, 2.26)**
p trend			-				**0.04**

[a] Adjusted for age, education, ethnicity, ever oral contraceptive use, number of live births, and other MVPA domains in table (respective to each time period).

[b] Adjusted for age, education, ethnicity, other MVPA domains in table (within each time period).

[c] Among pre-menopausal women, additionally adjusted for occupational MVPA during ages 35-49

[d] Among pre-menopausal women, additionally adjusted for occupational MVPA during ages 18-34

Chapter 5

Lifetime Physical Activity Associated with Breast Cancer Risk Defined by Estrogen, Progesterone, and Human Epidermal Growth Factor Receptor-2 Tumour Subtypes

5.1 Abstract

Background: Given that increased physical activity is associated with decreased breast cancer risk among post-menopausal women and that breast cancer is an increasingly heterogeneous disease, risk should be analyzed for effect modification using breast tumour subtype information. With a focus on moderate-to-vigourous intensity physical activity (MVPA), one of the few modifiable factors protective against breast cancer, we analysed risks for ER/PR-defined and ER/PR/HER2-defined breast tumours in a large case-control study in British Columbia, Canada.

Methods: Data from 632 cases and 623 controls, all post-menopausal, from a breast cancer case-control study of women aged 40-80 in Vancouver, British Columbia were used to analyse lifetime leisure-time, household, and occupational MVPA assessed by questionnaire. Mean metabolic equivalent (MET)-hours per week of each were calculated for age periods 12-17, 18-34, 35-49, and ≥50 years and the total lifetime. Odds ratios for risks of ER/PR-defined and ER/PR/HER2-defined breast tumours associated with MVPA from each domain across the life course were estimated using unconditional polytomous logistic regression.

Results: Lifetime leisure-time MVPA was associated with reduced risks for ER+ and/or PR+ (p_{trend}=0.006) and ER-/PR- tumours (p_{trend}=0.001). These effects appeared restricted to HER2- tumour subtypes (p_{trend}=0.002), although case-case analyses showed no difference at individual

MVPA exposure levels. Lifetime household MVPA reduced risk for ER+ and/or PR+ tumours (p_{trend}=0.0009), regardless of HER2 status. Occupational MVPA performed during ages ≥50 increased risks of ER-/PR- and ER-/PR-/HER2- breast tumours over two-fold with exposure-response relationships (p_{trend}=0.04 and 0.03, respectively) not observed for other tumour subtypes.

Conclusions: Leisure-time and household MVPA performed across the life course reduce breast cancer risk. We observed notable differences between tumour subtypes, suggesting the effects of leisure-time MVPA may be restricted to HER2- tumours. This relationship warrants further corroboration for understanding of etiology of HER2- tumours.

5.2 Introduction

The estrogen receptor (ER) and progesterone receptor (PR) are markers of breast tumour subtypes with differing risk factor profiles. Several hormonal reproductive factors appear to affect risk for hormone receptor-positive tumours more strongly than for receptor-negative tumours (1). By comparison, younger age, African ancestry, and BRCA1 gene mutations are risk factors more strongly associated with hormone receptor-negative tumours (2,3). Moderate-to-vigourous intensity physical activity (MVPA), one of the few modifiable factors that reduces breast cancer risk, remains of uncertain relationship to ER/PR+ and ER-/PR- breast tumours.

MVPA is a complex construct. Comprehensive MVPA measurement must account for energy expenditure dose (amount of time spent engaged in activity per specified unit of time, usually day or week), domain of activity (e.g., leisure-time, household, or occupational activity), and timing in life when activity was accrued (of particular importance given the long and uncertain latency period of breast cancer). Eight previous studies of post-menopausal women

have found no evidence for heterogeneity in risk for ER/PR+ and ER-/PR- tumours associated with physical activity (4-11), while three found stronger protective effects for hormone receptor-positive tumours (12-14), and one found stronger protective effects for receptor-negative tumours (15). These studies have used disparate methods of physical activity measurement with most examining recreational/sport/leisure-time activity at narrow lifetime exposure periods, which may partly explain inconsistent results. Only two studies examined MVPA from leisure-time, household, and occupational domains over the life course on risks for ER/PR-defined breast cancer, finding no evidence for heterogeneity (4,6).

Some epidemiological evidence indicates HER2 may be an additional marker of breast tumour etiologic heterogeneity, where some known risk factors for ER-/PR- breast tumours have been found to also apply to HER2- tumours (16-18). Whether HER2 is a relevant marker of etiologic heterogeneity of breast tumours with respect to MVPA is unknown. Two studies have examined MVPA in relation to risk for ER/PR/HER2-defined breast tumours among post-menopausal women, both examining leisure-time activity at narrow lifetime periods of exposure (12,19). One examined risk heterogeneity by HER2 status within ER/PR+ tumours and the other examined ER-/PR-/HER2- vs. ER+ tumours, both finding risk reductions (12,19).

Determination of whether MVPA is differentially associated with ER/PR-defined and ER/PR/HER2-defined subtypes will aid in understanding the biological mechanisms whereby MVPA reduces breast cancer risk. Effects of MVPA on sex hormones are thought to reduce risk for ER and PR positive tumours, while effects of MVPA on insulin, insulin-like growth factors, adipokines, and inflammatory markers may affect breast cancer risk independent of sex hormones (20). Whether HER2 is implicated in any of these mechanisms is unknown. Further, if MVPA is identified as particularly protective against any one tumour subtype, then women

known to be at high risk for that tumour subtype based on presence of other risk factors (e.g., BRCA1 gene mutations and African ancestry are risk factors for ER-/PR-/HER2- breast tumours) may particularly benefit from MVPA for breast cancer prevention. Further research with high-quality physical activity assessment is warranted to determine the role of HER2 in the anti-breast carcinogenic effects of MVPA and for the development of targeted MVPA interventions to prevent breast cancer among specific groups of women.

We sought to determine the independent effects of leisure-time, household, and occupational MVPA across the life course on risk for ER/PR-defined and ER/PR/HER2-defined post-menopausal breast cancer.

5.3 Methods

5.3.1 Study Population

The Molecular Epidemiology of Breast Cancer (MEBC) is a case-control study of women aged 40-80 with no previous cancer history (except non-melanoma skin cancer) in British Columbia (BC) conducted from 2006-2010. Methods and study population have been described previously (21). In brief, eligible incident invasive and *in situ* breast cancer cases residing in Vancouver, Richmond, Burnaby, and New Westminster were recruited from the BC Cancer Registry. Controls residing in the same geographic area were randomly selected from women enrolled in the Screening Mammography Program of BC (SMP BC) who had previously consented to contact for research studies during their last mammographic screening.

1,011 incident breast cancer cases and 1,014 controls were recruited and consented, with response rates of 54% for cases and 57% for controls. Participants completed a detailed questionnaire with responses recorded through telephone interview with a trained interviewer in English, Chinese, or Punjabi as needed, and most provided a blood sample and consent to

access medical records. 632 cases and 623 controls were classified as post-menopausal and had complete physical activity and covariate data and were included in this analysis. Ethics approval for this study was received from the University of British Columbia/BC Cancer Agency Research Ethics Board and the Queen's University Health Sciences Research Ethics Board.

5.3.2 MVPA Exposure Assessment

MVPA exposure assessment in the MEBC study has been described previously (22). In brief, regularly performed leisure-time, household, and occupational activity across the lifetime was measured in an open-ended questionnaire adapted from the Total Lifetime Physical Activity Questionnaire (23). This questionnaire is reliable, with test-retest Pearson's correlation coefficients of 0.72, 0.77, and 0.87 for lifetime leisure-time, household, and occupational activity, respectively, estimated in a study population similar to ours (23). Leisure-time, household, and occupational MVPA energy expenditures were summarized using metabolic equivalent (MET) scoring. MET scores, defined as the ratio of the calculated metabolic rate for a specific activity compared to resting metabolic rate, were abstracted from the Compendium of Physical Activities for each reported activity (24). Mean MET-hrs/week of energy expended in each activity domain were calculated for the adolescent (12-17 years), early adult (18-34 years), middle adult (34-49 years), and late adult (≥50 years) age periods, with the exception of occupational activity for the adolescent period. Lifetime MET-hrs/week of activity was subsequently determined for each activity domain by weighting the four age periods by the number of weeks lived during each age period.

5.3.3 Breast Cancer Outcome Assessment

Diagnostic and pathology data for breast cancer cases were obtained from the BC Cancer Registry and Breast Cancer Outcomes Unit. These data were used to classify breast

tumour subtype for each breast cancer case first by ER and PR status as ER+ and/or PR+ (referred to from here on as ER/PR+) or ER-/PR-. These two case groups were further stratified by HER2 status to create four tumour groups: ER+ and/or PR+/HER2- (referred to from here on as ER/PR+/HER2-); ER+ and/or PR+/HER2+ (referred to from here on as ER/PR+/HER2+); ER-/PR-/HER2+; or ER-/PR-/HER2-. ER and PR statuses were determined using immunohistochemistry (IHC), each classified into one of six categories: OZER = negative (0/3), OLOW = weakly positive (1/3), OMOD = moderately positive (2/3), OHIG = strongly positive (3/3), OXXX = receptors tested but not sufficient quantity for interpretation or borderline/equivocal and XXXX = not tested. Tumours were considered ER or PR positive if classified as OLOW, OMOD or OHIG.

HER2 status was determined using IHC, or, if IHC produced indeterminable results, using fluorescence *in situ* hybridization (FISH). Using IHC, tumours were classified into one of seven categories: 0 = negative, 1 = weak staining (+1), 2 = moderate staining (+2; equivocal, indeterminate), 3 = strong staining (+3), 4 = positive, not quantified, 8 = not done/not applicable, 9 = done, result unknown. Using FISH, tumours were classified into one of six categories: 33 = indeterminate result (ratio >4.0 and < 8.0), 44 = negative (ratio ≤ 4.0), 55 = positive (ratio ≥ 8.0), 66 = negative, ratio not given, 77 = positive, ratio not given, 88 = not done/not applicable, 99 = done, result unknown. Tumours were considered HER2 positive if classified as 1, 3, or 4 with IHC, or, if classified as 55 or 77 using FISH.

5.3.4 Confounders

Suspected confounders measured by self-report in the study questionnaire are: age (continuous), ethnicity (European, Chinese, or Other), education level (secondary school or less, college diploma or trade certificate, undergraduate degree, or graduate or professional degree), primary family history of breast cancer (yes or no), age at menarche (continuous), ever pregnant

(yes or no), number of live births (0, 1-3, ≥4), age at first pregnancy (continuous, among parous women only), ever breastfeeding (yes or no), ever oral contraceptive use (yes or no), ever hormone replacement therapy use (yes or no), lifetime pack-years of cigarette smoking (continuous), and mean weekly alcohol consumption (continuous; measured for total lifetime and specific to each age period examined). These are all known or suspected breast cancer risk factors plausibly associated with MVPA, or strong breast cancer risk factors warranting confounder assessment (25,26). Since obesity, which is typically assessed using the body mass index (BMI), is likely on the causal pathway between MVPA and breast cancer risk, it was not considered as a confounder.

5.3.5 Statistical Analysis

Classic descriptive statistics were used to compare case subtypes, first stratified by ER/PR status then by ER/PR/HER2 status, to controls. Polytomous logistic regression was used to estimate odds ratios (ORs) for the associations between leisure-time, household, and occupational MVPA across the total lifetime and during age periods with risk for breast cancer first stratified by ER/PR status (ER/PR+ and ER-/PR-) and then by ER/PR/HER2 status (ER/PR+/HER2-, ER/PR+/HER2+, ER-/PR-/HER2+, ER-/PR-/HER2-) in an exploratory analysis. Tertiles of non-zero values of mean MET-hrs/week of MVPA (based on distribution among controls) were compared to 0 MET-hrs/week of MVPA as the reference category. Potential confounders were included in initial models if they were associated with breast cancer (case vs. control) at $p \leq 0.20$, and retained in final models if their deletion changed OR estimates by ≥10% (27). Age, education, ethnicity, and MVPA were always included in modeling. Confounders were selected using unconditional logistic regression with a dichotomous case-control outcome and subsequently applied to polytomous logistic regression models. In a second set of models where

MVPA during each age period was adjusted for MVPA performed during other age periods of life, odds ratios were minimally changed (results not shown).

Case-case polytomous logistic regression analyses were performed to determine heterogeneity of ORs associated with MVPA between tumour subtypes, generating p-values for tumour heterogeneity (p_{TH}). These models were controlled for the same confounders as the case-control polytomous logistic regression models. For ER/PR-defined subtypes, ER/PR+ tumours served as the reference and for ER/PR/HER2-defined subtypes, ER/PR+/HER2- tumours served as the reference. Sensitivity analyses were performed excluding cases who reported never having a mammogram or having their first mammogram <1 year prior to breast cancer diagnosis (n=67). Excluded cases were non-differential by tumour subgroup. Results were similar to the overall analyses and subsequently are not presented. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

5.4 Results

5.4.1 Descriptive Characteristics

Compared to ER/PR+ and ER-/PR- cases, controls were more likely to be of European ethnicity, have higher education, lower BMI, and drank more alcohol per week on average, while both ER/PR+ and ER-/PR- cases were more likely to have a primary family history of breast cancer (Table 5.1). Controls and ER-/PR- cases were more likely than ER/PR+ cases to have ever used oral contraceptives, and ER-/PR- cases were younger on average than ER/PR+ cases (Table 5.1). When cases were further stratified by HER2 status, the same case-control differences remained (Table 5.2). ER-/PR-/HER2- cases were younger than controls and ER/PR+/HER2- cases, and ER-/PR-/HER2+ cases were younger than ER/PR+/HER2- cases (Table 5.2). ER-/PR-/HER2-

cases drank less alcohol on average across the lifetime and after age 50 than other case subtypes.

5.4.2 Lifetime MVPA and ER/PR-defined Breast Cancer

Table 5.3 shows odds ratios (ORs) for the associations between total lifetime leisure-time, household, and occupational MVPA and risk of ER/PR+ and ER-/PR- breast cancers. Lifetime leisure-time MVPA was associated with reduced risks for ER/PR+ and ER-/PR- breast cancers (ER/PR+ p_{trend}=0.06; ER-/PR- p_{trend}=0.001). Lifetime household MVPA was associated with reduced risk of ER/PR+, but not ER-/PR- breast cancer (ER/PR+ p_{trend}=0.0009; ER-/PR- p_{trend}=0.17). Lifetime occupational MVPA was not associated with risk for either tumour subgroup. Case-case polytomous logistic regression models showed no differences between individual ORs for ER/PR+ and ER-/PR- tumour subgroups for all three activity domains.

5.4.3 MVPA by Age Period and ER/PR-defined Breast Cancer

Table 5.4 shows MVPA domains broken down by age period and risk for ER/PR+ and ER-/PR- breast cancers. Patterns of association with leisure-time MVPA between tumour subgroups were most consistent during ages 35-49 (ER/PR+ p_{trend}=0.003; ER-/PR- p_{trend}=0.0008) and ≥50 (ER/PR+ p_{trend}=0.01; ER-/PR- p_{trend}=0.01). Household MVPA performed during adulthood was consistently associated with reduced risk for ER/PR+ breast tumours (p_{trend} for ages 18-34=0.004; p_{trend} for ages 35-49=0.003; p_{trend} for ages ≥50=0.0008), but not ER-/PR- tumours (Table 5.4). Across most age periods, occupational MVPA was associated with slight non-significant increases in ER/PR+ and ER-/PR- breast cancer risk, although high occupational activity performed during ages ≥50 was associated with a two-fold increase for ER-/PR- breast cancer risk (OR=2.01; 95% CI: 1.23-3.31, p_{trend}=0.04). Despite differences in exposure-response relationships, case-case polytomous logistic regression models showed no differences between

ORs at individual levels of MVPA exposure for ER/PR+ and ER-/PR- tumour subgroups for all three activity domains.

5.4.4 Lifetime MVPA and ER/PR/HER2-defined Breast Cancer

Table 5.5 shows results for the analysis of total lifetime leisure-time, household, and occupational MVPA and risk of ER/PR/HER-defined breast cancers. Risk reductions associated with lifetime leisure-time MVPA were restricted to HER2- tumour subtypes: ER/PR+/HER2- p_{trend}=0.002 and ER-/PR-/HER2- p_{trend}=0.002. Lifetime household MVPA was associated with reduced risks of ER/PR+/HER2- (p_{trend}=0.005) and ER/PR+/HER2+ (p_{trend}=0.06), but not ER-/PR-/HER2+ or ER-/PR-/HER2- breast tumours. ORs for lifetime occupational activity generally showed slight non-statistically significant increases in risk for ER/PR/HER2-defined tumour subgroups, and no exposure-response relationships were detected. Case-case polytomous logistic regression models showed no differences between ORs for ER/PR/HER2-defined tumour subgroups for all three activity domains.

5.4.5 MVPA by Age Period and ER/PR/HER2-defined Breast Cancer

Table 5.6 shows results for the exploratory analysis of MVPA domains broken down by age period and risk for ER/PR/HER2-defined breast cancers. Leisure-time MVPA was associated with risk reductions for ER/PR+/HER2- and ER-/PR-/HER2- breast cancers during ages 35-49 (ER/PR+/HER2- p_{trend}=0.004; ER-/PR-/HER2- p_{trend}=0.002) and ≥50 (ER/PR+/HER2- p_{trend}=0.005; ER-/PR-/HER2- p_{trend}=0.04).

Household MVPA performed during ages 18-34, 35-49, and ≥50 was associated with both ER/PR+/HER2- and ER/PR+/HER2+ breast tumours in a similar fashion as with ER/PR+ breast tumours, although p_{trend} for ER/PR+/HER2+ tumours did not reach statistical significance for ages 18-34 (Table 5.6). Household MVPA during ages ≥50 was associated with stronger OR

point estimates for ER/PR+/HER2+ tumours than for ER/PR+/HER2- tumours, and case-case polytomous logistic regression analysis confirmed this stronger effect among receptor-positive tumours (p_{TH} for tertile 2=0.03; p_{TH} for tertile 3=0.04).

Occupational MVPA was not associated with risk for any tumour subgroup across age periods, with the exception of ages ≥50, where occupational MVPA was associated with increased risk of ER-/PR-/HER2- tumours with p_{trend}=0.03 (Table 5.6). With the exception of household MVPA during ages 35-49 and ≥50, case-case polytomous logistic regression models showed no differences between individual ORs for ER/PR/HER2-defined tumour subgroups for all three activity domains.

5.5 Discussion

This study examined independent effects of leisure-time, household, and occupational MVPA across the life course on risk for ER/PR-defined breast cancer, and in an exploratory analysis, ER/PR/HER-defined breast cancer among post-menopausal women. Lifetime leisure-time MVPA had similar effects on ER/PR+ and ER-/PR- breast tumour subtypes, with respective risk reductions of 40% and 70% observed for the highest activity groups. When further stratified by HER2 status, these effects appeared confined to HER2- tumour subgroups, although case-case analyses detected no difference between tumour subtypes at individual levels of MVPA exposure. Household MVPA during adulthood age periods reduced risk for ER/PR+ tumours regardless of HER2 status, although when performed beyond age 50, reduced risk for HER2+ tumours more strongly than for HER2- tumours. High occupational MVPA performed beyond age 50 increased risk of ER-/PR-/HER2- breast tumours.

Our results for ER/PR-defined breast tumours are comparable with two studies examining leisure-time, household, and occupational MVPA by age period across the life course

in relation to these tumour subgroups, finding no evidence for tumour heterogeneity across activity domains and lifetime periods (4,6). A study of physical activity during ages 13-19 and the past 10 years only also found no heterogeneity in risk by ER/PR tumour status (9). We additionally found that household MVPA performed during adulthood reduces risk for ER/PR+ tumours more strongly than for ER-/PR- tumours, although effects were protective for both subtypes. Other studies examining physical activity and ER/PR tumour status have examined recreational (8,10,11,13-15) or baseline (5) activity only, resulting in loss of exposure information. The MARIE case-control study in Germany, found leisure-time activity performed after age 50 to reduce risk for ER/PR+ breast tumours, but not ER-/PR- tumours (12). This study recorded participation in walking, cycling, and sports only in their assessment of leisure-time activity, and subsequently may not have recorded all relevant types of leisure-time activity (12). Another prospective study of leisure-time activity found reduced risk for ER/PR+ tumours with activity performed ≥3 days/week, although the authors did not provide p-values for heterogeneity between tumour subgroups (14).

MVPA is thought to affect post-menopausal breast cancer risk primarily through direct and indirect reductions in systemic sex hormones (28). The ALPHA trial of post-menopausal women in Alberta, Canada found that MVPA performed 45 minutes per day, 5 days per week reduces circulating estradiol and increases sex hormone binding globulin levels, changes partially mediated by adiposity reduction (29,30). Thus, MVPA plausibly reduces risk for ER+ breast tumours, which are dependent on estrogen. The protective effects we and other studies have observed on ER-/PR- breast tumours are possibly explained by other biologic mechanisms. MVPA improves insulin metabolism, affects adipokines, and reduces inflammatory markers associated with obesity (31-34), all of which are thought to have direct protective effects against

breast cancer independent of sex hormones (35-37). MVPA may reduce systemic levels of certain insulin-like growth factors (IGFs) and their binding proteins (IGFBPs), although randomized and observational evidence for these effects is limited (34,38,39). Thus, MVPA may have protective effects on both ER/PR+ and ER-/PR- negative breast tumours through different biological mechanisms.

Our results for ER/PR/HER2-defined breast tumours build on those of two previous studies (12,19). The first, the German MARIE study, examined risk of ER/PR+/HER2+ versus ER/PR+/HER2- breast cancer associated with leisure-time activity, finding similar odds ratios for both subtypes (12). The second study used prospective U.S. Women's Health Initiative data, finding similar protective hazards ratios between ER+ and ER-/PR-/HER2- tumours (19). PR and HER2 status were disregarded within the ER+ category defined by the investigators, and subsequently some tumour heterogeneity may have been present within this category. Both studies examined leisure-time activity only over narrow time windows of exposure (≥50 years for the MARIE study and baseline activity in the Women's Health Initiative).

Since these studies each compared two tumour subtypes, our results comparing four subtypes are difficult to consider with theirs, although risk reductions were observed by both studies and ours. In our exploratory analysis, we found that protective effects of lifetime MVPA may be restricted to HER2- tumour subtypes. Risk reductions associated with household MVPA during ages 35-49 and ≥50 were stronger for ER/PR+/HER2+ tumours than for ER/PR+/HER2- tumours. Our finding of a two-fold increase in risk for ER-/PR-/HER2- breast cancer with occupational MVPA after age 50 may be due to occupational breast cancer risk factors associated with job intensity not examined here. Although ER and HER2 expression are

correlated (40), biologic plausibility for the implication of HER2 in the effects of MVPA on breast cancer prevention remains to be established.

This study is the first to examine independent effects of leisure-time, household, and occupational MVPA across the life course on risk for ER/PR/HER2-defined breast cancer. MVPA in each domain was adjusted for MVPA in other domains, and we found no changes in results when MVPA at specific age periods was adjusted for MVPA at other age periods across the life course. Our comprehensive questionnaire minimized loss of physical activity exposure information and misclassification, as we were able to account for all lifetime activity reported for leisure-time, household, and occupational domains. Although our questionnaire was self-report, it is reliable. We do not expect recall bias to have occurred, as the physical activity questionnaire was part of a larger questionnaire, although non-differential recall error may have resulted in our findings to underestimate the true effects of physical activity on breast cancer risk.

Since cases were recruited from the BC cancer registry and controls were recruited from the provincial mammographic screening program, some cases in our study population may not have been eligible to be controls had they not developed breast cancer. However, in sensitivity analyses excluding all cases unlikely to have undergone routine mammographic screening, results were unchanged. Another concern for potential selection bias is the relatively low response rates. However, response rates were non-differential by case-control status, and we have no reason to expect response was related to physical activity. The distribution of breast tumour subgroups within cases reflects the distribution observed in other case groups (17), indicating that response was not related to breast tumour subgroup. Our study was not able to detect small differences in odds ratios and associated 95% confidence intervals between tumour

subgroups; however, most odds ratios were in the protective direction and indicate physical activity is overall beneficial to breast cancer risk reduction. Although we lacked adequate numbers to detect effects among the most rare tumour subgroup, the ER-/PR-/HER2+ subgroup, no other study has examined risk for this tumour subtype associated with physical activity.

In conclusion, this study demonstrates protective effects of leisure-time and household MVPA, particularly during adulthood, on risks for ER/PR-defined and ER/PR/HER2-defined post-menopausal breast cancer. An increase in risk for triple-negative breast cancer associated with occupational MVPA performed after age 50 may be due to occupational exposures requiring further investigation. Our findings indicate HER2 may be implicated in the anti-breast carcinogenic effects of leisure-time physical activity, although corroboration of our findings is required, especially in larger studies. As the current body of evidence stands, MVPA appears generally protective against breast cancer risk and should be emphasized for prevention of post-menopausal breast cancer. Further understanding of the biological mechanisms whereby MVPA reduces breast cancer risk will advance knowledge of breast carcinogenesis and its prevention, and aid in development of MVPA interventions targeting breast cancer prevention.

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Table 5.1 Characteristics of study population, cases stratified by ER/PR status					
	Controls (n=623) n %	ER/PR+ (n=485) n %	ER-/PR- (n=147) n %	p_{CC} *	p_{TH} §
Age (mean ±SD)	62.8±8.0	63.1±8.2	60.9±8.0	**0.02**[a]	**0.006**[b]
Education					
High School or less	183 (29)	172 (42)	27 (35)	**<0.0001**[c]	0.90[c]
College Degree/Certificate	180 (29)	109 (27)	27 (35)		
Bachelor's Degree	131 (21)	86 (21)	15 (19)		
Graduate/Professional Degree	129 (20)	40 (10)	9 (11)		
Ethnicity					
European	493 (79)	306 (63)	90 (61)	**<0.0001**[c]	0.37[c]
Chinese	55 (9)	95 (20)	36 (24)		
Other	75 (12)	84 (17)	21 (14)		
BMI					
Underweight/Normal (≤24.99)	356 (57)	233 (48)	75 (51)	**0.007**[c]	0.56[c]
Overweight (25.00 – 29.99)	185 (30)	161 (33)	42 (28)		
Obese (≥30.00)	75 (12)	87 (18)	29 (20)		
Missing	7 (1)	4 (1)	2 (1)		
1° family hx of breast cancer					
Yes	86 (14)	98 (20)	35 (24)	**0.002**[c]	0.35[c]
No	537 (86)	387 (80)	112 (76)		
Age at menarche (mean±SD)	12.8±1.5	13.0±1.7	12.9±1.4	0.26[a]	0.41[b]
Ever oral contraceptive use					
Yes	370 (59)	238 (49)	88 (60)	**0.01**[c]	0.06[c]
No	253 (41)	247 (51)	59 (40)		
Ever pregnant					
Yes	508 (82)	405 (84)	122 (84)	0.61[c]	0.68[c]
No	115 (18)	80 (16)	23 (16)		
Age at 1st pregnancy[*] (mean ±SD)	26.2±4.4	26.3±4.9	25.6±4.7	0.31[a]	0.15[b]
Number of live births					
0	161 (26)	114 (24)	28 (19)	0.23[c]	0.16[c]
1-3	415 (67)	328 (68)	111 (76)		
≥4	47 (8)	43 (9)	8 (5)		
Ever breastfeeding					
Yes	359 (58)	280 (58)	74 (50)	0.24[c]	0.11[c]
No	264 (42)	205 (42)	73 (50)		
Ever HRT Use					
Yes	297 (48)	223 (46)	63 (43)	0.61[c]	0.59[c]
No	325 (52)	262 (54)	82 (57)		
Lifetime smoking pack-years (mean±SD)	6.9±23.0	6.7±13.3	7.2±15.9	0.70[d]	0.47[d]
Alcoholic drinks/week (mean±SD)					
Lifetime	3.3±4.6	3.0±6.2	1.9±3.0	**<0.0001**[d]	**0.04**[d]
Adolescence (ages 12-17)	1.2±3.5	0.91±3.8	0.37±1.2	**<0.0001**[d]	0.07[d]
Early adulthood (ages 18-34)	3.4±6.2	2.8±6.4	1.9±3.3	**<0.0001**[d]	0.21[d]
Middle adulthood (ages 35-49)	3.4±5.2	3.4±7.4	2.1±3.6	**<0.0001**[d]	0.05[d]
Late adulthood (ages ≥50)	3.7±6.3	3.1±5.5	2.0±3.7	**<0.0001**[d]	**0.03**[d]

[*] p_{CC} = p case-control; p-value for comparison of characteristics between case subtypes and controls

[§] p_{TH} = p tumour heterogeneity; p-value for comparison of characteristics between case subtypes

[a] One-way ANOVA

[b] Student's t-test

[c] Chi-square test

[d] Kruskal-Wallis test

Table 5.2 Characteristics of study population, cases stratified by ER/PR/HER2 status

	Controls (n=623) n (%)	ER/PR+/ HER2- (n=407) n (%)	ER/PR+/ HER2+ (n=78) n (%)	ER-/PR- /HER2+ (n=31) n (%)	ER-/PR- /HER2- (n=116) n %	p_{CC} *	p_{TH} §
Age (mean ±SD)	62.8±8.0	63.3±8.3	61.6±7.7	60.3±8.2	61.1±8.0	**0.03**[a]	**0.014**[a]
Education							
High School or less	183 (29)	172 (42)	27 (35)	12 (39)	50 (43)	**0.0001**[b]	0.83[b]
College Degree/Certificate	180 (29)	109 (27)	27 (35)	10 (32)	31 (27)		
Bachelor's Degree	131 (21)	86 (21)	15 (19)	4 (13)	23 (20)		
Graduate/Professional Degree	129 (20)	40 (10)	9 (11)	5 (16)	12 (10)		
Ethnicity							
European	493 (79)	259 (64)	47 (60)	20 (65)	70 (60)	**<0.0001**[b]	0.44[b]
Chinese	55 (9)	83 (20)	12 (15)	7 (23)	29 (25)		
Other	75 (12)	65 (16)	19 (24)	4 (13)	17 (15)		
BMI							
Underweight/Normal (≤24.99)	356 (57)	193 (48)	40 (51)	13 (43)	62 (53)	**0.009**[b]	0.31[b]
Overweight (25.00 – 29.99)	185 (30)	140 (34)	21 (27)	13 (43)	29 (25)		
Obese (≥30.00)	75 (12)	70 (17)	17 (22)	4 (13)	25 (22)		
Missing	7 (1)	4 (1)	-	1 (1)	-		
1° family history of breast cancer							
Yes	86 (14)	81 (20)	17 (22)	10 (32)	25 (22)	**0.006**[b]	0.44[b]
No	537 (86)	326 (80)	61 (78)	21 (68)	91 (78)		
Age at menarche (mean±SD)	12.8±1.5	13.0±1.7	12.7±1.8	13.1±1.6	12.8±1.4	0.19[a]	0.29[a]
Ever oral contraceptive use							
Yes	370 (59)	203 (50)	44 (56)	22 (71)	66 (57)	**0.02**[b]	0.08[b]
No	253 (41)	204 (50)	34 (44)	9 (29)	50 (43)		
Ever pregnant							
Yes	508 (82)	338 (83)	67 (86)	28 (90)	94 (82)	0.66[b]	0.68[b]
No	115 (18)	69 (17)	11 (14)	3 (10)	20 (18)		
Age at 1st pregnancy* (mean ±SD)	26.2±4.4	26.4±4.9	25.7±4.9	26.4±4.7	25.4±4.7	0.29[a]	0.22[a]
Number of live births							
0	161 (26)	91 (22)	23 (29)	3 (10)	25 (22)	0.27[b]	0.23[b]
1-3	415 (67)	279 (69)	49 (63)	27 (87)	84 (72)		
≥4	47 (8)	37 (9)	6 (8)	1 (3)	7 (6)		
Ever breastfeeding							
Yes	359 (58)	235 (57)	45 (58)	18 (58)	56 (48)	0.43[b]	0.33[b]
No	264 (42)	172 (42)	33 (42)	13 (42)	60 (52)		
Ever HRT Use							
Yes	297 (48)	224 (55)	38 (49)	15 (48)	48 (42)	0.66[b]	0.63[b]
No	325 (52)	183 (45)	40 (51)	16 (52)	66 (58)		
Lifetime smoking pack-yrs (mean±SD)	6.9±23.0	6.4±12.6	8.5±16.2	6.3±14.0	7.5±16.4	0.66[c]	0.51[c]
Alcoholic drinks/week (mean±SD)							
Lifetime	3.3±4.6	3.0±6.6	2.7±3.4	3.0±3.9	1.6±2.7	**<0.0001**[c]	**0.03**[c]
Adolescence (ages 12-17)	1.2±3.5	0.95±4.13	0.69±1.5	0.49±1.5	0.34±1.2	**0.0005**[c]	0.22[c]
Early adulthood (ages 18-34)	3.4±6.2	2.7±6.7	3.0±4.5	2.7±3.6	1.7±3.2	**<0.0001**[c]	0.17[c]
Middle adulthood (ages 35-49)	3.4±5.2	3.5±4.7	3.0±4.7	3.5±4.7	1.8±3.1	**<0.0001**[c]	0.05[c]
Late adulthood (ages ≥50)	3.7±6.3	3.2±5.7	2.8±3.9	3.6±4.9	1.6±3.3	**<0.0001**[c]	**0.02**[c]

* p_{CC} = p case-control; p-value for comparison of descriptive characteristics between case subtypes and controls

§ p_{TH} = p tumour heterogeneity; p-value for comparison of descriptive characteristics between case subtypes

[a] One-way ANOVA

[b] Chi-square test

[c] Kruskal-Wallis test

Table 5.3 Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between lifetime MVPA and risk for ER/PR-defined post-menopausal breast cancer

Lifetime MVPA (mean MET-hrs/wk)	Controls (n=623) n %	ER/PR+ (n=485)		ER-/PR- (n=147)		p_{TH} [§]
		n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	
Leisure-time						
0 MET-hrs/wk	67 (11)	72 (15)	1.00 (reference)	27 (18)	1.00 (reference)	
≤8.5	183 (29)	189 (39)	1.09 (0.73, 1.64)	53 (36)	0.72 (0.41, 1.27)	0.13
8.51 – 24.9	182 (29)	140 (29)	0.97 (0.63, 1.49)	46 (31)	0.72 (0.40, 1.29)	0.33
>24.9	191 (31)	84 (17)	**0.61 (0.39, 0.96)**	21 (14)	**0.33 (0.17, 0.66)**	0.10
p trend			**0.006**		**0.001**	
Household						
0 MET-hrs/wk	159 (25)	172 (35)	1.00 (reference)	47 (32)	1.00 (reference)	
≤24.8	153 (25)	105 (22)	0.74 (0.52, 1.05)	38 (26)	1.02 (0.61, 1.69)	0.18
24.8 – 79.5	153 (25)	122 (25)	0.82 (0.58, 1.14)	31 (21)	0.83 (0.49, 1.40)	0.99
>79.5	158 (25)	86 (17)	**0.51 (0.36, 0.73)**	31 (21)	0.72 (0.42, 1.21)	0.23
p trend			**0.0009**		0.17	
Occupational						
0 MET-hrs/wk	263 (42)	184 (38)	1.00 (reference)	54 (37)	1.00 (reference)	
≤33.6	118 (19)	91 (23)	1.22 (0.86, 1.72)	29 (20)	1.27 (0.75, 2.13)	0.95
33.61 – 95.0	120 (19)	112 (23)	**1.48 (1.06, 2.08)**	29 (20)	1.23 (0.73, 2.06)	0.43
>95.0	122 (20)	98 (20)	1.21 (0.86, 1.72)	35 (24)	1.39 (0.84, 2.31)	0.68
p trend			0.10		0.19	

* Adjusted for age, education, ethnicity, and other domains of lifetime MVPA in table

§ p_{TH} = p for tumour heterogeneity; obtained from logistic regression analysis comparing ER-/PR- breast cancer to ER/PR+ as the reference, controlled for all factors listed in the first footnote

Table 5.4 Adjusted ORs (95% CI) for the association between MVPA by age period and risk for ER/PR-defined post-menopausal breast cancer

MVPA (mean MET-hrs/wk)	Controls (n=623) n %	ER/PR+ (n=485)		ER-/PR- (n=147)		p_{TH} §
		n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	
Leisure-time						
12 – 17 years						
0 MET-hrs/wk	188 (30)	187 (39)	1.00 (reference)	48 (33)	1.00 (reference)	
≤15.0	144 (23)	119 (25)	0.95 (0.69, 1.32)	42 (29)	1.23 (0.76, 1.99)	0.27
15.01 – 39.6	143 (23)	103 (21)	0.92 (0.65, 1.29)	37 (25)	1.31 (0.79, 2.17)	0.17
>39.6	148 (24)	76 (16)	**0.67 (0.47, 0.97)**	20 (14)	0.71 (0.39, 1.29)	0.80
p trend			**0.04**		0.51	
18 – 34 years						
0 MET-hrs/wk	201 (32)	175 (36)	1.00 (reference)	66 (45)	1.00 (reference)	
≤7.0	139 (22)	144 (30)	**1.41 (1.02, 1.94)**	37 (25)	0.92 (0.58, 1.48)	0.07
7.01 – 22.0	139 (22)	100 (21)	1.14 (0.80, 1.62)	25 (17)	0.67 (0.39, 1.15)	0.05
>22.0	144 (23)	66 (14)	0.77 (0.53, 1.31)	19 (13)	**0.51 (0.28, 0.92)**	0.22
p trend			0.27		**0.01**	
35 – 49 years						
0 MET-hrs/wk	213 (34)	229 (47)	1.00 (reference)	79 (54)	1.00 (reference)	
≤9.2	134 (21)	108 (22)	0.93 (0.67, 1.30)	28 (19)	0.61 (0.37, 1.02)	0.14
9.21 – 27.6	136 (22)	89 (18)	0.83 (0.59, 1.18)	24 (16)	0.57 (0.33, 0.97)	0.19
>27.6	140 (22)	59 (12)	**0.54 (0.37, 0.79)**	16 (11)	**0.38 (0.20, 0.70)**	0.36
p trend			**0.003**		**0.0008**	
≥50 years‡						
0 MET-hrs/wk	174 (28)	181 (39)	1.00 (reference)	61 (44)	1.00 (reference)	
≤8.8	141 (23)	110 (24)	0.83 (0.59, 1.17)	25 (18)	**0.56 (0.33, 0.96)**	0.09
8.81 – 26.2	142 (23)	110 (24)	0.92 (0.66, 1.29)	35 (25)	0.88 (0.54, 1.43)	0.77
>26.2	147 (24)	64 (14)	**0.56 (0.38, 0.82)**	17 (12)	**0.40 (0.22, 0.73)**	0.27
p trend			**0.01**		**0.01**	
Household						
12 – 17 years						
0 MET-hrs/wk	523 (84)	414 (85)	1.00 (reference)	125 (85)	1.00 (reference)	
≤10.2	33 (5)	16 (3)	0.77 (0.41, 1.44)	8 (5)	1.20 (0.53, 2.73)	0.30
10.21 – 41.7	33 (5)	27 (6)	1.16 (0.67, 1.99)	7 (5)	0.96 (0.41, 2.28)	0.77
>41.7	34 (6)	28 (6)	1.02 (0.60, 1.73)	7 (5)	0.84 (0.36, 1.98)	0.66
p trend			0.87		0.78	
18 – 34 years						
0 MET-hrs/wk	192 (31)	209 (43)	1.00 (reference)	57 (39)	1.00 (reference)	
≤29.9	142 (23)	86 (18)	**0.67 (0.47, 0.95)**	30 (20)	0.86 (0.51, 1.44)	0.31
29.9 – 99.7	142 (23)	87 (18)	**0.61 (0.43, 0.87)**	27 (18)	0.73 (0.43, 1.24)	0.52
>99.7	147 (24)	103 (21)	**0.65 (0.46, 0.90)**	33 (22)	0.80 (0.48, 1.31)	0.51
p trend			**0.004**		0.28	
35 – 49 years						
0 MET-hrs/wk	200 (32)	219 (45)	1.00 (reference)	62 (42)	1.00 (reference)	
≤26.9	139 (22)	85 (18)	**0.65 (0.46, 0.92)**	28 (19)	0.76 (0.45, 1.27)	0.58
26.91 – 114.3	139 (22)	85 (18)	**0.58 (0.41, 0.82)**	31 (21)	0.78 (0.47, 1.28)	0.32
>114.3	145 (23)	96 (20)	**0.65 (0.47, 0.91)**	26 (18)	0.64 (0.38, 1.08)	0.88
p trend			**0.003**		0.10	
≥50 years‡						
0 MET-hrs/wk	284 (47)	287 (62)	1.00 (reference)	85 (62)	1.00 (reference)	
≤8.1	104 (17)	53 (11)	**0.58 (0.40, 0.85)**	13 (9)	**0.51 (0.27, 0.97)**	0.61
8.11 – 67.0	107 (18)	73 (16)	0.82 (0.58, 1.17)	22 (16)	0.87 (0.51, 1.49)	0.89
>67.0	109 (18)	52 (11)	**0.50 (0.34, 0.73)**	18 (13)	0.61 (0.34, 1.08)	0.44

p trend			**0.0008**		0.11	
Occupational						
18 – 34 years						
0 MET-hrs/wk	344 (55)	270 (56)	1.00 (reference)	79 (54)	1.00 (reference)	
≤46.9	92 (15)	66 (14)	1.09 (0.75, 1.57)	25 (17)	1.35 (0.80, 2.28)	0.44
46.91 – 95.2	88 (14)	64 (13)	1.11 (0.77, 1.60)	24 (16)	1.29 (0.76, 2.19)	0.53
>95.2	99 (16)	85 (18)	1.08 (0.76, 1.54)	19 (13)	0.78 (0.44, 1.39)	0.26
p trend			0.56		0.73	
35 – 49 years						
0 MET-hrs/wk	363 (58)	26 (54)	1.00 (reference)	74 (50)	1.00 (reference)	
≤68.4	86 (14)	65 (13)	1.01 (0.70, 1.47)	27 (18)	1.43 (0.85, 2.40)	0.17
68.41 – 138.6	86 (14)	86 (18)	**1.54 (1.08, 2.20)**	21 (14)	1.21 (0.69, 2.12)	0.39
>138.6	88 (14)	71 (15)	1.00 (0.69, 1.45)	25 (17)	1.20 (0.70, 2.04)	0.51
p trend			0.31		0.38	
≥50 years[‡]						
0 MET-hrs/wk	385 (64)	276 (59)	1.00 (reference)	81 (59)	1.00 (reference)	
≤64.0	72 (12)	67 (14)	1.22 (0.83, 1.79)	15 (11)	1.01 (0.54, 1.90)	0.51
64.01 – 102.3	72 (12)	45 (10)	0.91 (0.59, 1.38)	9 (7)	0.60 (0.29, 1.28)	0.27
>102.3	75 (12)	77 (17)	1.45 (1.00, 2.11)	33 (24)	**2.01 (1.23, 3.31)**	0.25
p trend			0.10		**0.04**	

[*] Adjusted for age, education, ethnicity, and other MVPA domains in table (within each time period)

[§] p_{TH} = p for tumour heterogeneity; obtained from logistic regression analysis comparing ER-/PR- breast cancer to ER/PR+ as the reference, controlled for all factors listed in the first footnote

[‡] 603 cases and 604 controls (389 ER^+ and/or $PR^+/HER2^-$; 76 ER^+ and/or $PR^+/HER2^+$; 27 $ER^-/PR^-/HER2^+$; 111 $ER^-/PR^-/HER2^-$; participants ≥50 years old included only)

Table 5.5 Adjusted ORs (95% CI) for the association between lifetime MVPA and risk for ER/PR/HER2-defined breast cancer among post-menopausal women

MVPA (mean MET-hrs/week)	Controls (n=623) n (%)	ER/PR+/HER2- (n=407)		ER/PR+/HER2+ (n=78)			ER-/PR-/HER2+ (n=31)			ER-/PR-/HER2- (n=116)		
		n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	p_{TH} §	n (%)	OR (95% CI)*	p_{TH} §	n (%)	OR (95% CI)*	p_{TH} §
Leisure-time												
0 MET-hrs/wk	67 (11)	61 (15)	1.0 (reference)	11 (14)	1.0 (reference)	-	5 (16)	1.0 (reference)	-	22 (19)	1.0 (reference)	-
≤8.5	183 (29)	163 (40)	1.11 (0.73, 1.70)	26 (33)	1.01 (0.46, 2.21)	0.81	11 (35)	0.80 (0.26, 2.46)	0.47	42 (36)	0.70 (0.38, 1.30)	0.14
8.51 – 24.9	182 (29)	120 (29)	0.99 (0.64, 1.55)	20 (26)	0.89 (0.39, 2.05)	0.81	9 (29)	0.71 (0.22, 2.34)	0.58	37 (31)	0.71 (0.38, 1.36)	0.36
>24.9	191 (31)	63 (16)	**0.55 (0.34, 0.89)**	21 (27)	0.97 (0.41, 2.29)	0.20	6 (19)	0.51 (0.14, 1.88)	0.89	15 (13)	**0.29 (0.14, 0.64)**	0.14
p trend			**0.002**		0.81			0.26			**0.002**	
Household												
0 MET-hrs/wk	159 (25)	141 (35)	1.0 (reference)	31 (40)	1.0 (reference)	-	9 (29)	1.0 (reference)	-	38 (33)	1.0 (reference)	-
≤24.8	153 (25)	87 (21)	0.76 (0.52, 1.10)	18 (23)	0.69 (0.36, 1.32)	0.84	7 (23)	0.94 (0.33, 2.68)	0.59	31 (26)	1.04 (0.60, 1.81)	0.23
24.8 – 79.5	153 (25)	103 (25)	0.84 (0.59, 1.21)	19 (24)	0.69 (0.36, 1.29)	0.62	6 (19)	0.81 (0.28, 2.38)	0.99	25 (21)	0.84 (0.47, 1.48)	0.90
>79.5	158 (25)	76 (19)	**0.52 (0.38, 0.80)**	10 (13)	**0.33 (0.16, 0.72)**	0.23	9 (29)	1.07 (0.40, 2.87)	0.19	22 (19)	0.63 (0.35, 1.14)	0.70
p trend			**0.005**		**0.006**			0.95			0.11	
Occupational												
0 MET-hrs/wk	263 (42)	156 (38)	1.00 (reference)	28 (36)	1.00 (reference)	-	12 (39)	1.00 (reference)	-	42 (36)	1.00 (reference)	-
≤33.6	118 (19)	77 (19)	1.22 (0.84, 1.75)	14 (18)	1.25 (0.62, 2.49)	0.99	5 (16)	0.96 (0.33, 2.86)	0.63	24 (21)	1.36 (0.77, 2.39)	0.78
33.61 – 95.0	120 (19)	100 (25)	**1.56 (1.10, 2.22)**	12 (15)	1.03 (0.50, 2.13)	0.29	9 (29)	1.59 (0.63, 3.98)	0.93	20 (17)	1.11 (0.61, 2.01)	0.22
>95.0	122 (20)	74 (18)	1.10 (0.76, 1.60)	24 (31)	1.74 (0.94, 3.22)	0.17	5 (16)	0.84 (0.28, 2.52)	0.52	30 (26)	1.56 (0.91, 2.68)	0.25
p trend			0.19		0.12			0.89			0.15	

*Adjusted for age, ethnicity, education, leisure-time, household, and occupational MVPA (within each time period).

§ p_{TH} = p for tumour heterogeneity; from case-case polytomous logistic regression model comparing each tumour subtype to ER+/PR+/HER2- with same covariates as the polytomous case-control regression model

Table 5.6 Adjusted ORs (95% CI) for the association between MVPA by age period and risk for ER/PR/HER2-defined breast cancer among post-menopausal women												
MVPA (mean MET-hrs/week)	Controls (n=623)	ER/PR+/HER2- (n=407)		ER/PR+/HER2+ (n=78)			ER-/PR-/HER2+(n=31)			ER-/PR-/HER2- (n=116)		
		n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	p_{TH} §	n (%)	OR (95% CI)*	p_{TH} §	n (%)	OR (95% CI)*	p_{TH} §
Leisure-time												
12-17 years												
0 MET-hrs/wk	188 (30)	157 (39)	1.00 (reference)	30 (38)	1.00 (reference)	-	11 (35)	1.00 (reference)	-	37 (33)	1.00 (reference)	-
≤15.0	144 (23)	103 (25)	0.99 (0.70, 1.39)	16 (21)	0.77 (0.40, 1.49)	0.45	7 (23)	0.87 (0.32, 2.35)	0.81	35 (30)	1.33 (0.79, 2.26)	0.24
15.01 – 39.6	143 (23)	81 (20)	0.85 (0.59, 1.22)	22 (28)	1.29 (0.70, 2.39)	0.22	7 (23)	1.05 (0.38, 2.88)	0.71	30 (25)	1.39 (0.80, 2.42)	0.09
>39.6	148 (24)	66 (16)	0.69 (0.47, 1.01)	10 (13)	0.59 (0.27, 1.28)	0.77	6 (19)	0.91 (0.31, 2.64)	0.61	14 (12)	0.65 (0.33, 1.29)	0.96
p trend			0.05		0.48			0.92			0.47	
18-34 years												
0 MET-hrs/wk	201 (32)	147 (36)	1.00 (reference)	28 (36)	1.00 (reference)	-	11 (35)	1.00 (reference)	-	55 (47)	1.00 (reference)	-
≤7.0	139 (22)	119 (29)	1.38 (0.98, 1.93)	25 (32)	1.55 (0.86, 2.83)	0.68	10 (32)	1.46 (0.59, 3.62)	0.96	27 (23)	0.81 (0.48, 1.37)	0.05
7.01 – 22.0	139 (22)	89 (22)	1.22 (0.85, 1.76)	11 (14)	0.73 (0.34, 1.57)	0.20	6 (19)	0.90 (0.31, 2.59)	0.45	19 (16)	0.63 (0.34, 1.14)	**0.03**
>22.0	144 (23)	52 (13)	0.74 (0.49, 1.10)	14 (18)	0.95 (0.46, 1.96)	0.46	4 (13)	0.59 (0.17, 2.04)	0.74	15 (13)	**0.50 (0.26, 0.95)**	0.31
p trend			0.54		0.31			0.36			**0.01**	
35-49 years												
0 MET-hrs/wk	213 (34)	191 (47)	1.00 (reference)	38 (49)	1.00 (reference)	-	15 (48)	1.00 (reference)	-	64 (55)	1.00 (reference)	-
≤9.2	134 (21)	93 (23)	0.98 (0.69, 1.38)	15 (19)	0.75 (0.39, 1.45)	0.47	6 (19)	0.67 (0.25, 1.83)	0.51	22 (19)	0.60 (0.35, 1.05)	0.13
9.21 – 27.6	136 (22)	77 (19)	0.88 (0.61, 1.26)	12 (15)	0.63 (0.31, 1.29)	0.34	8 (26)	0.94 (0.37, 2.42)	0.79	16 (14)	**0.48 (0.26, 0.88)**	0.06
>27.6	140 (22)	46 (11)	**0.51 (0.34, 0.78)**	13 (17)	0.66 (0.32, 1.36)	0.50	2 (13)	0.23 (0.05, 1.06)	0.39	14 (12)	**0.42 (0.22, 0.81)**	0.65
p trend			**0.004**		0.16			0.11			**0.002**	
≥50 years ǂ												
0 MET-hrs/wk	174 (28)	152 (39)	1.00 (reference)	29 (38)	1.00 (reference)	-	11 (41)	1.00 (reference)	-	50 (45)	1.00 (reference)	-
≤8.8	141 (23)	94 (24)	0.85 (0.60, 1.21)	16 (21)	0.75 (0.38, 1.45)	0.81	7 (26)	0.82 (0.30, 2.20)	0.92	18 (16)	**0.50 (0.27, 0.92)**	0.05
8.81 – 26.2	142 (23)	93 (24)	0.93 (0.65, 1.32)	17 (22)	0.91 (0.47, 1.75)	0.97	5 (19)	0.61 (0.20, 1.85)	0.50	30 (27)	0.94 (0.56, 1.60)	0.93
>26.2	147 (24)	50 (13)	**0.52 (0.34, 0.77)**	14 (18)	0.80 (0.39, 1.62)	0.26	4 (15)	0.46 (0.14, 1.53)	0.88	13 (12)	**0.38 (0.19, 0.75)**	0.35
p trend			**0.005**		0.73			0.10			**0.04**	
Household												
12-17 years												
0 MET-hrs/wk	523 (84)	344 (85)	1.00 (reference)	70 (90)	1.00 (reference)	-	27 (87)	1.00 (reference)	-	98 (84)	1.00 (reference)	-
≤10.2	33 (5)	12 (3)	0.70 (0.35, 1.39)	4 (5)	1.17 (0.39, 3.47)	0.39	1 (3)	0.65 (0.08, 5.06)	0.99	7 (6)	1.37 (0.58, 3.28)	0.16
10.21 – 41.7	33 (5)	26 (6)	1.36 (0.78, 2.35)	1 (1)	0.24 (0.03, 1.77)	0.10	1 (3)	0.60 (0.08, 4.61)	0.49	6 (5)	1.06 (0.42, 2.67)	0.66
>41.7	34 (6)	25 (6)	1.11 (0.64, 1.93)	3 (4)	0.58 (0.17, 1.98)	0.37	2 (6)	1.05 (0.23, 4.72)	0.98	5 (4)	0.78 (0.29, 2.07)	0.47
p trend			0.51		0.18			0.80			0.84	

18-34 years												
0 MET-hrs/wk	192 (31)	173 (43)	1.00 (reference)	36 (46)	1.00 (reference)	-	11 (36)	1.00 (reference)	-	46 (40)	1.00 (reference)	-
≤29.9	142 (23)	75 (18)	0.72 (0.50, 1.03)	11 (14)	0.47 (0.23, 0.98)	0.30	8 (26)	1.08 (0.41, 2.81)	0.32	22 (19)	0.80 (0.45, 1.43)	0.65
29.91 – 99.7	142 (23)	72 (18)	**0.62 (0.43, 0.89)**	15 (19)	0.58 (0.30, 1.12)	0.82	4 (12)	0.54 (0.17, 1.78)	0.86	23 (20)	0.78 (0.44, 1.37)	0.46
>99.7	147 (24)	87 (21)	**0.66 (0.46, 0.93)**	16 (21)	0.59 (0.31, 1.11)	0.64	8 (26)	1.06 (0.41, 2.75)	0.38	25 (21)	0.73 (0.42, 1.28)	0.84
p trend			**0.008**		0.08			0.81			0.26	
35-49 years												
0 MET-hrs/wk	200 (32)	182 (45)	1.00 (reference)	37 (47)	1.00 (reference)	-	11 (35)	1.00 (reference)	-	52 (44)	1.00 (reference)	-
≤26.9	139 (22)	71 (17)	**0.65 (0.45, 0.94)**	14 (18)	0.64 (0.33, 1.26)	0.94	4 (13)	0.57 (0.17, 1.86)	0.80	24 (21)	0.81 (0.47, 1.40)	0.47
26.91 – 114.3	139 (22)	70 (17)	**0.58 (0.40, 0.83)**	15 (19)	0.61 (0.32, 1.17)	0.78	7 (23)	0.99 (0.37, 2.68)	0.29	24 (21)	0.73 (0.42, 1.27)	0.47
>114.3	145 (23)	84 (21)	**0.68 (0.48, 0.96)**	12 (15)	0.50 (0.25, 1.00)	0.42	9 (29)	1.26 (0.50, 3.18)	0.22	17 (15)	**0.51 (0.30, 0.93)**	0.31
p trend			**0.008**		**0.04**			0.54			**0.03**	
≥50 years ‡												
0 MET-hrs/wk	284 (47)	233 (60)	1.00 (reference)	54 (71)	1.00 (reference)	-	15 (56)	1.00 (reference)	-	70 (63)	1.00 (reference)	-
≤8.1	104 (17)	41 (11)	**0.56 (0.37, 0.85)**	12 (16)	0.71 (0.36, 1.40)	0.62	2 (7)	0.39 (0.09, 1.76)	0.61	11 (10)	0.55 (0.28, 1.10)	0.85
8.11 – 67.0	107 (18)	67 (17)	0.95 (0.66, 1.37)	6 (8)	**0.34 (0.14, 0.84)**	**0.03**	6 (22)	1.28 (0.48, 3.44)	0.42	16 (14)	0.80 (0.43, 1.47)	0.47
>67.0	109 (18)	48 (12)	**0.58 (0.39, 0.86)**	4 (5)	**0.19 (0.07, 0.55)**	**0.04**	4 (15)	0.71 (0.23, 2.21)	0.84	14 (13)	0.59 (0.31, 1.13)	0.80
p trend			**0.02**		**0.0002**			0.77			0.10	
Occupational												
18-34 years												
0 MET-hrs/wk	344 (55)	231 (57)	1.00 (reference)	39 (50)	1.00 (reference)	-	18 (58)	1.00 (reference)	-	61 (53)	1.00 (reference)	-
≤46.9	92 (15)	53 (13)	1.04 (0.70, 1.53)	13 (17)	1.40 (0.70, 2.77)	0.45	3 (10)	0.68 (0.19, 2.40)	0.49	22 (19)	1.46 (0.81, 2.62)	0.18
46.91 – 95.2	88 (14)	53 (13)	1.10 (0.75, 1.62)	11 (14)	1.16 (0.56, 2.40)	0.88	5 (16)	1.15 (0.41, 3.27)	0.90	19 (16)	1.39 (0.79, 2.43)	0.48
>95.2	99 (16)	70 (17)	1.03 (0.71, 1.50)	15 (19)	1.32 (0.69, 2.54)	0.58	5 (16)	0.94 (0.33, 2.65)	0.82	14 (12)	0.76 (0.40, 1.45)	0.31
p trend			0.72		0.42			0.97			0.71	
35-49 years												
0 MET-hrs/wk	363 (58)	224 (55)	1.00 (reference)	224(55)	1.00 (reference)	-	17 (55)	1.00 (reference)	-	57 (49)	1.00 (reference)	-
≤68.4	86 (14)	58 (14)	1.06 (0.72, 1.57)	58 (14)	0.72 (0.31, 1.69)	0.40	6 (19)	1.29 (0.48, 3.46)	0.62	21 (18)	1.48 (0.83, 2.61)	0.24
68.41 – 138.6	86 (14)	70 (17)	**1.51 (1.03, 2.20)**	70 (17)	1.70 (0.89, 3.25)	0.68	5 (16)	1.20 (0.42, 3.46)	0.55	16 (14)	1.22 (0.65, 2.27)	0.55
>138.6	88 (14)	55 (14)	0.92 (0.62, 1.36)	55 (14)	1.43 (0.75, 2.74)	0.23	3 (10)	0.65 (0.18, 2.30)	0.55	22 (19)	1.35 (0.77, 2.39)	0.18
p trend			0.55		0.12			0.72			0.23	
≥50 years ‡												
0 MET-hrs /wk	385 (64)	237 (61)	1.00 (reference)	39 (51)	1.00 (reference)	-	15 (56)	1.00 (reference)	-	66 (59)	1.00 (reference)	-
≤64.0	72 (12)	54 (14)	1.12 (0.75, 1.68)	13 (17)	1.86 (0.92, 3.75)	0.16	3 (11)	1.15 (0.32, 4.18)	0.99	12 (11)	0.98 (0.49, 1.94)	0.68
64.01 – 102.3	72 (12)	34 (9)	0.80 (0.50, 1.26)	11 (15)	1.52 (0.73, 3.19)	0.08	6 (22)	2.19 (0.80, 6.0)	0.06	3 (3)	0.25 (0.07, 0.81)	0.06
>102.3	75 (12)	64 (16)	1.42 (0.96, 2.10)	13 (17)	1.70 (0.85, 3.42)	0.57	3 (11)	0.98 (0.27, 3.53)	0.06	30 (27)	**2.25 (1.33, 3.80)**	0.11
p trend			0.25		0.05			0.68			**0.03**	

[*] Adjusted for age, ethnicity, education, leisure-time, household, and occupational MVPA (within each time period).

[§] p_{TH} = p for tumour heterogeneity; from case-case polytomous logistic regression model comparing each tumour subtype to ER+/PR+/HER2- with same covariates as the polytomous case-control regression model

[‡] 603 cases and 604 controls (389 ER^+ and/or $PR^+/HER2^-$; 76 ER^+ and/or $PR^+/HER2^+$; 27 $ER^-/PR^-/HER2^+$; 111 $ER^-/PR^-/HER2^-$; participants ≥50 years old included only)

Chapter 6

Additional Results

This chapter contains additional results not found in Chapters 4 and 5. Section 6.1 is comprised of descriptive results from objective 1. Section 6.2 displays the results for objective 3 for pre-menopausal women, which are parallel to those shown for post-menopausal women in the Chapter 5 manuscript. The results for pre-menopausal women are limited by lack of statistical power and were subsequently excluded from the manuscript.

6.1 Descriptive MVPA Results

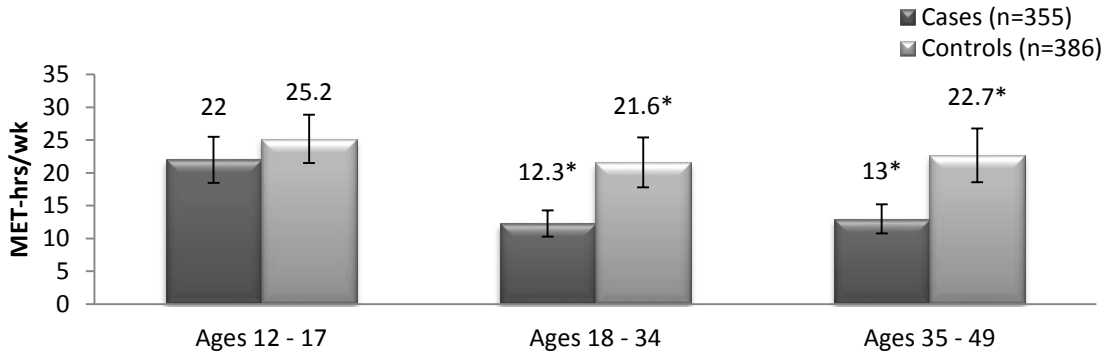
Objective 1 of this thesis, "To describe lifetime moderate-to-vigourous physical activity energy expenditure cumulatively and over four age periods of exposure for pre- and post-menopausal cases and controls", does not directly map onto a manuscript for publication. Chapters 4 and 5 of this thesis show descriptive MVPA results directly relevant to those manuscripts, while additional descriptive results are presented here.

6.1.1 Mean MVPA across the Life Course

Figures 6.1 and 6.2 show mean MET-hrs/week of leisure-time MVPA across the life course for pre- and for post-menopausal women, respectively. Mean leisure-time MVPA was significantly different between cases and controls for adulthood time periods (ages 18-34 and 35-49) among pre-menopausal women, and for all time periods among post-menopausal women. The Wilcoxon rank-sum test was used to compare means. Qualitatively, pre-menopausal cases appeared more physically active during adolescence than during adulthood,

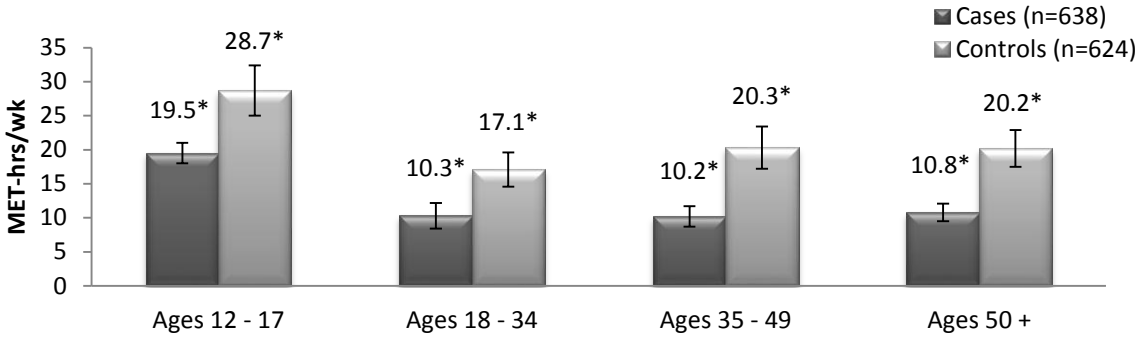
while controls maintained similar mean MVPA levels throughout all age periods. MET-hrs/week values of 22.0 (cases) and 25.2 (controls) for the 12-17 age period are approximately equivalent to 4-5 hours/week of active gym classes or team sports. Among post-menopausal women, cases and controls appeared more physically active during adolescence than during adulthood. Mean MET-hrs/week of leisure-time MVPA appeared similar between menopausal groups.

Figure 6.1 Mean MET-hrs/wk of leisure-time MVPA among pre-menopausal women



Error bars show 95% CI around the mean. * indicates means for cases and controls significantly different at $p<0.05$.

Figure 6.2 Mean MET-hrs/wk of leisure-time MVPA among post-menopausal women



Error bars show 95% CI around the mean. * indicates means for cases and controls significantly different at $p<0.05$.

Figure 6.3 shows mean MET-hrs/week of household MVPA across the life course for pre-menopausal women and Figure 6.4 shows mean MET-hrs/week of household MVPA across the life course for post-menopausal women.

Figure 6.3 Mean MET-hrs/week of household MVPA among pre-menopausal women

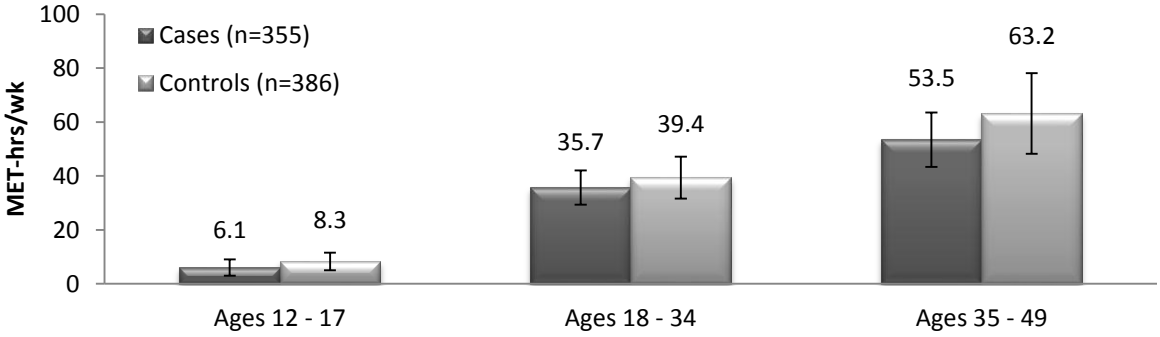
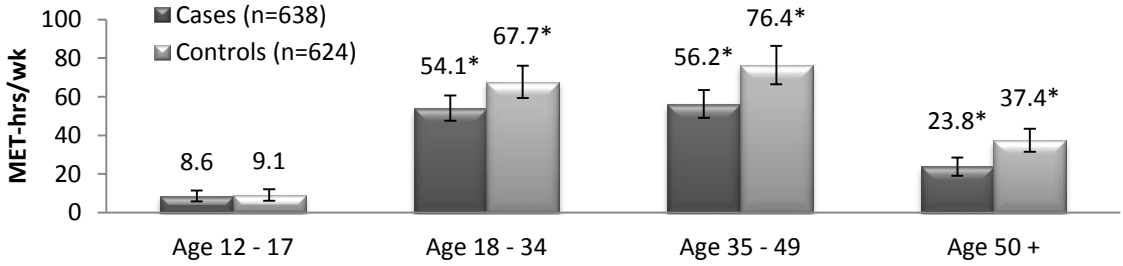


Figure 6.4 Mean MET-hrs/week of household MVPA among post-menopausal women



Mean MET-hrs/week of household MVPA did not differ between cases and controls at any age period among pre-menopausal women. MET-hrs/week values of 6.1 (cases) and 8.3 (controls) for the 12-17 age period are approximately equivalent to 3 hours per week of household chores, such as preparing food or dusting. MET-hrs/week values of 53.5 (cases) and 63.5 (controls) for the 35-49 age period are approximately equivalent to 21.5 and 25.5 hours/week, respectively, of household chores. Among post-menopausal women, mean household MVPA was significantly different between cases and controls during ages 18-34, 35-

49, and ≥50. Among both pre- and post-menopausal women, cases and controls performed relatively very little household MVPA during adolescence, with mean weekly household MVPA increasing at ages 18-34 and 35-49.

Figure 6.5 shows mean MET-hrs/week of occupational MVPA across the life course for pre-menopausal women and Figure 6.6 shows mean MET-hrs/week of occupational MVPA across the life course for post-menopausal women.

Figure 6.5 Mean MET-hrs/week of occupational MVPA among pre-menopausal women

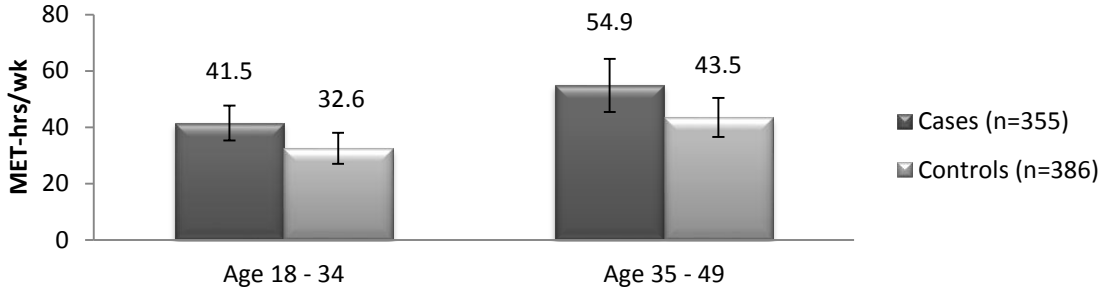
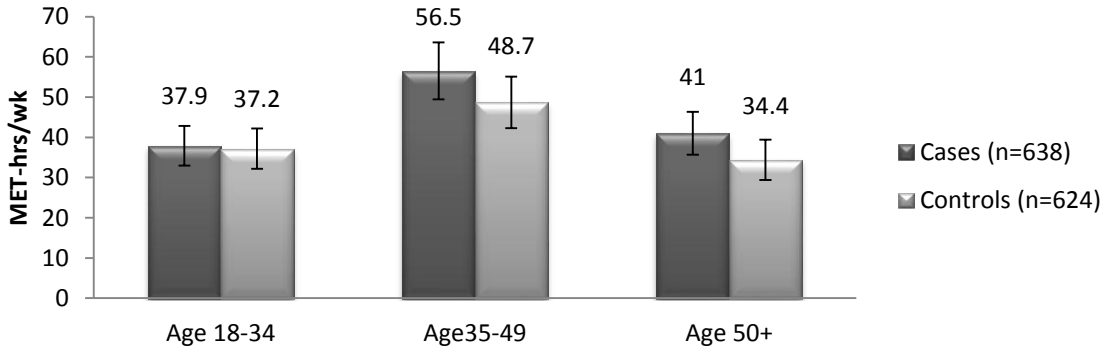


Figure 6.6 Mean MET-hrs/week of occupational MVPA among post-menopausal women



Although mean MET-hrs/week of occupational MVPA was higher among cases than controls among both pre- and post-menopausal women for all time periods, these differences were not statistically significant. Mean weekly levels of occupational MVPA were highest for both pre- and post-menopausal women during ages 35-49. Mean MET-hrs/values of 56.5 (cases)

and 48.7 (controls) calculated for the 35-49 age period among post-menopausal women are approximately equivalent to 19 and 16 hours/week, respectively, of a job involving continuous walking and lifting of light objects.

6.1.2 Correlation of MVPA across Lifetime Exposure Periods

Spearman's rank correlation coefficients were calculated for mean MET-hrs/week of MVPA in each activity domain across age periods. Table 6.1 shows Spearman's rho for mean MET-hrs/week of MVPA performed at different age periods among pre-menopausal women. Leisure-time MVPA performed during ages 12-17 was moderately positively correlated with MVPA performed during ages 18-34 and weakly positively correlated with MVPA during ages 35-49. Adolescent household MVPA and adulthood household MVPA (ages 18-34 and 35-49) were not well correlated, although statistically significant. Household MVPA performed during ages 18-34 and 35-49 were strongly positively correlated (Spearman's rho=0.71; $p<0.001$). Occupational MVPA during ages 18-34 and 35-49 were moderately positively correlated.

Table 6.1 Correlations between MVPA across age periods: pre-menopausal women*

	Adolescence (12-17)	Early Adulthood (18-34)	Middle Adulthood (35-49)
a) Leisure-time MVPA			
Adolescence (12-17)	-	0.47	0.25
Early Adulthood (18-34)	-	-	0.61
Middle Adulthood (35-49)	-	-	-
b) Household MVPA			
Adolescence (12-17)	-	0.27	0.15
Early Adulthood (18-34)	-	-	0.71
Middle Adulthood (35-49)	-	-	-
c) Occupational MVPA			
Early Adulthood (18-34)	-	-	0.56
Middle Adulthood (18-34)	-	-	-

*Spearman's rho; all p<0.0001

Table 6.2 shows Spearman's rho for mean MET-hrs/week of MVPA at different age periods among post-menopausal women. Leisure-time MVPA performed during ages 12-17 was moderately positively correlated with leisure-time MVPA performed during ages 18-34 and weakly positively correlated with leisure-time MVPA performed during ages 35-49 and ≥50. Leisure-time MVPA performed during ages 18-34, 35-49, and ≥50 were strongly positively correlated with each other. Household MVPA performed during ages 12-17 was weakly positively correlated with household MVPA in all other time periods of life. Household MVPA performed during ages 18-34 and 35-49 were strongly positively correlated (Spearman's rho=0.77; $p<0.001$). Household MVPA performed during ages 18-34 and 35-49 were each moderately positively correlated with household MVPA performed ≥50. Occupational MVPA during ages 35-49 and ≥50 were strongly positively correlated, while occupational MVPA during ages 18-34 and ≥50 were moderately positively correlated.

Table 6.2 Correlations between MVPA across age periods: post-menopausal women*

	Adolescence (12-17)	Early Adulthood (18-34)	Middle Adulthood (35-49)	Late Adulthood (≥50)
a) Leisure-time MVPA				
Adolescence (12-17)	-	0.52	0.27	0.21
Early Adulthood (18-34)	-	-	0.65	0.40
Middle Adulthood (35-49)	-	-	-	0.65
Late Adulthood (50+)	-	-	-	-
b) Household MVPA				
Adolescence (12-17)	-	0.22	0.13	0.18
Early Adulthood (18-34)	-	-	0.77	0.42
Middle Adulthood (35-49)	-	-	-	0.59
Late Adulthood (50+)	-	-	-	-
c) Occupational MVPA				
Early Adulthood (18-34)	-	-	0.61	0.43
Middle Adulthood (35-49)	-	-	-	0.70
Late Adulthood (50+)	-	-	-	-

*Spearman's rho; all $p<0.0001$

6.1.3 Correlation of MVPA across Domains

Spearman's rank correlation coefficients were calculated for mean MET-hrs/week of MVPA in each lifetime period across leisure-time, household, and occupational domains. Table 6.3 shows the correlation coefficients for pre-menopausal women. Across lifetime periods, leisure-time, household, and occupational MVPA were weakly positively correlated, or not correlated. Total lifetime MVPA across three activity domains was significantly correlated, but with weak positive magnitude.

Table 6.3 Correlations between MVPA across domains: pre-menopausal women

	Leisure-time MVPA	Household MVPA	Occupational MVPA
Adolescence (ages 12-17)			
Leisure-time MVPA	-	0.13; *p*=0.0003	-
Household MVPA	-	-	-
Early Adulthood (ages 18-34)			
Leisure-time MVPA	-	0.01; *p*=0.75	0.11; *p*=0.003
Household MVPA	-	-	0.07; *p*=0.06
Occupational MVPA	-	-	-
Middle Adulthood (ages 35-49)			
Leisure-time MVPA	-	0.06; *p*=0.12	-0.05; *p*=0.14
Household MVPA	-	-	0.08; *p*=0.03
Occupational MVPA	-	-	-
Total Lifetime			
Leisure-time MVPA	-	0.08; *p*=0.04	0.09; *p*=0.02
Household MVPA	-	-	0.13; *p*<0.0001
Occupational MVPA	-	-	-

Table 6.4 shows correlation coefficients for post-menopausal women. Again, across all lifetime periods, MVPA domains were weakly positively correlated or not correlated. Total lifetime MVPA across three activity domains was significantly correlated, but with weak positive magnitude.

Table 6.4 Correlations between MVPA across domains: post-menopausal women			
	Leisure-time MVPA	Household MVPA	Occupational MVPA
Adolescence (ages 12-17)			
Leisure-time MVPA	-	0.14; $p<0.0001$	-
Household MVPA	-	-	-
Occupational MVPA	-	-	-
Early Adulthood (ages 18-34)			
Leisure-time MVPA	-	0.05; $p=0.10$	0.07; $p=0.02$
Household MVPA	-	-	0.08; $p=0.007$
Occupational MVPA	-	-	-
Middle Adulthood (ages 35-49)			
Leisure-time MVPA	-	0.10; $p=0.0006$	0.03; $p=0.35$
Household MVPA	-	-	0.05; $p=0.07$
Occupational MVPA	-	-	-
Late Adulthood (ages ≥50)			
Leisure-time MVPA	-	0.17; $p<0.0001$	0.03; $p=0.41$
Household MVPA	-	-	0.11; $p=0.0001$
Occupational MVPA	-	-	-
Total Lifetime			
Leisure-time MVPA	-	0.11; $p<0.0001$	0.10; $p=0.0007$
Household MVPA	-	-	0.13; $p<0.0001$
Occupational MVPA	-	-	-

6.2 MVPA and Risk for Breast Tumour Subgroups among Pre-menopausal Women

This section presents results for pre-menopausal women for objective 3 of this thesis. Table 6.5 shows descriptive characteristics of pre-menopausal cases and controls, with cases stratified into ER/PR+ and ER-/PR- subgroups. Controls were more likely to be of European ethnicity, were more likely to have used oral contraceptives, and drank more alcohol per week on average than ER/PR+ or ER-/PR- cases. Cases and controls were similar on all other characteristics, and no differences were observed between ER/PR+ and ER-/PR- cases.

Table 6.6 shows descriptive characteristics of pre-menopausal cases and controls, with cases stratified into ER/PR+/HER2-, ER/PR+/HER2+, ER-/PR-/HER2+, and ER-/PR-/HER2- subgroups. Controls were significantly older than ER/PR+/HER2+ cases, but there were no differences with other case subgroups. Additionally, controls were more likely to be European ethnicity, to have used oral contraceptives, and drank more alcohol on average per week than all case subgroups. Cases and controls were similar on all other characteristics, and no differences were observed between ER/PR+/HER2-, ER/PR+/HER2+, ER-/PR-/HER2+, and ER-/PR-/HER2- case subgroups.

Table 6.5 Characteristics of pre-menopausal women, cases stratified by ER/PR status					
	Controls (n=384) n %	ER/PR+ (n=277) n %	ER-/PR- (n=78) n %	p_{CC} *	p_{TH} §
Age (mean±SD)	47.3±3.7	47.0±3.9	46.8±4.2	0.44[a]	0.69[b]
Education					
High School or less	60 (16)	63 (23)	15 (19)	0.16[c]	0.59[c]
College Degree/Certificate	115 (30)	82 (29)	29 (37)		
Bachelor's Degree	135 (35)	91 (33)	25 (32)		
Graduate/Professional Degree	74 (19)	41 (15)	9 (12)		
Ethnicity					
European	263 (68)	140 (51)	40 (51)	**<0.0001**[c]	0.90[c]
Chinese	57 (15)	81 (29)	24 (31)		
Other	64 (17)	56 (20)	14 (18)		
BMI					
Underweight/Normal (≤24.99)	248 (64)	182 (66)	53 (68)	0.45[c]	0.69[c]
Overweight (25.00 – 29.99)	86 (23)	68 (25)	17 (22)		
Obese (≥30.00)	46 (12)	21 (8)	8 (10)		
Missing	4 (1)	6 (1)	0 (0)		
1° family hx of breast cancer					
Yes	48 (12)	46 (17)	15 (19)	0.17[c]	0.59[c]
No	336 (88)	231 (83)	63 (81)		
Age at menarche (mean±SD)	12.8±1.5	12.7±1.4	12.9±1.4	0.61[a]	0.44[b]
Ever oral contraceptive use					
Yes	277 (72)	154 (56)	37 (47)	**<0.0001**[c]	0.20[c]
No	107 (28)	123 (44)	41 (53)		
Ever pregnant					
Yes	277 (72)	220 (79)	65 (83)	0.03[c]	0.44[c]
No	107 (28)	57 (21)	13 (17)		
Age at 1st pregnancy* (mean ±SD)	28.0±5.1	28.2±4.9	27.7±4.9	0.71[a]	0.45[b]
Number of live births					
0	147 (38)	87 (31)	20 (26)	0.014[c]	0.53[d]
1-3	223 (58)	187 (68)	57 (73)		
≥4	14 (4)	3 (1)	1 (1)		
Ever breastfeeding					
Yes	213 (55)	156 (56)	51 (65)	0.27[c]	0.15[c]
No	171 (45)	121 (44)	27 (35)		
Lifetime smoking pack-years (mean±SD)	5.1±35.6	2.8±7.0	3.6±7.5	0.88[e]	0.95[f]
Alcoholic drinks/week (mean±SD)					
Lifetime	3.7±5.0	2.4±3.8	2.5±4.0	**<0.0001**[e]	0.61[f]
Adolescence (ages 12-17)	2.1±4.2	0.81±2.2	1.5±4.4	**<0.0001**[e]	0.24[f]
Early adulthood (ages 18-34)	4.2±7.1	2.4±4.2	3.2±5.6	**<0.0001**[e]	0.95[f]
Middle adulthood (ages 35-49)	3.7±5.1	2.6±4.1	2.3±4.0	**<0.0001**[e]	0.32[f]

* p_{CC} = p case-control; p-value for comparison of characteristics between case subtypes and controls

§ p_{TH} = p tumour heterogeneity; p-value for comparison of characteristics between case subtypes

[a] One-way ANOVA

[b] Student's t-test

[c] Chi-square test

[d] Fisher's exact test

[e] Kruskal-Wallis test

[f] Wilcoxon rank-sum test

Table 6.6 Characteristics of pre-menopausal women, cases stratified by ER/PR/HER2 status

	Controls (n=384) n %	ER/PR+/ HER2- (n=224) n %	ER/PR+/ HER2+ (n=53) n %	ER-/PR- /HER2+ (n=17) n %	ER-/PR- /HER2- (n=61) n %	p_{CC} *	p_{TH} §
Age (mean±SD)	47.3±3.7	47.2±3.9	46.2±3.7	46.9±4.1	47.8±4.2	0.31[a]	0.38[a]
Education							
High School or less	60 (16)	49 (22)	14 (26)	4 (24)	11 (18)	0.24[b]	0.55[b]
College Degree/Certificate	115 (30)	64 (29)	19 (34)	8 (47)	21 (34)		
Bachelor's Degree	135 (35)	76 (34)	15 (28)	2 (12)	23 (38)		
Graduate/Professional Degree	74 (19)	35 (16)	6 (11)	3 (18)	6 (10)		
Ethnicity							
European	263 (68)	112 (50)	28 (53)	8 (47)	32 (52)	**0.0001**[b]	0.89[b]
Chinese	57 (15)	69 (31)	12 (23)	5 (29)	19 (31)		
Other	64 (17)	43 (19)	13 (24)	4 (24)	10 (16)		
BMI							
Underweight/Normal (≤24.99)	248 (64)	148 (66)	34 (64)	7 (41)	46 (75)	0.11[b]	0.07[c]
Overweight (25.00 – 29.99)	86 (23)	57 (26)	11 (21)	7 (41)	10 (16)		
Obese (≥30.00)	46 (12)	14 (6)	7 (13)	3 (18)	5 (8)		
Missing	4 (1)	5 (2)	1 (2)	0 (0)	0 (0)		
1° family history of breast cancer							
Yes	48 (12)	36 (16)	10 (19)	4 (24)	11 (18)	0.39[b]	0.85[b]
No	336 (88)	188 (84)	43 (81)	13 (77)	50 (82)		
Age at menarche (mean±SD)	12.8±1.5	12.7±1.4	12.8±1.4	12.8±1.3	12.9±1.4	0.89[a]	0.87[a]
Ever oral contraceptive use							
Yes	277 (72)	127 (57)	27 (51)	8 (47)	29 (48)	**<0.0001**[b]	0.53[b]
No	107 (28)	97 (43)	26 (49)	9 (53)	32 (52)		
Ever pregnant							
Yes	277 (72)	179 (80)	41 (77)	15 (88)	50 (82)	0.12[b]	0.78[b]
No	107 (28)	45 (20)	12 (23)	2 (12)	11 (18)		
Age at 1st pregnancy (mean±SD)	28.0±5.1	28.2±4.9	28.3±5.3	27.0±3.9	28.0±5.1	0.88[a]	0.78[a]
Number of live births							
0	147 (38)	71 (32)	16 (30)	4 (24)	16 (26)	0.11[b]	0.84[c]
1-3	223 (58)	151 (67)	36 (68)	13 (76)	44 (72)		
≥4	14 (4)	2 (1)	1 (2)	0 (0)	1 (2)		
Ever breastfeeding							
Yes	213 (55)	126 (56)	30 (57)	12 (71)	39 (64)	0.58[b]	0.51[b]
No	171 (45)	98 (44)	23 (43)	5 (29)	22 (36)		
Lifetime smoking pack-years (mean±SD)	5.1±35.6	3.0±7.3	2.4±5.2	4.7±9.3	3.2±7.0	0.97[d]	0.96[d]
Alcoholic drinks/week (mean±SD)							
Lifetime	3.7±5.0	2.4±3.6	2.4±4.6	2.5±3.4	2.5±4.2	**<0.0001**[d]	0.94[d]
Adolescence (ages 12-17)	2.1±4.2	1.5±4.5	1.5±4.0	1.1±3.5	0.7±1.7	**0.0006**[d]	0.65[d]
Early adulthood (ages 18-34)	4.2±7.1	2.4±3.9	2.7±5.4	2.7±4.3	3.3±5.9	**<0.0001**[d]	0.86[d]
Middle adulthood (ages 35-49)	3.7±5.1	2.6±4.1	2.4±4.1	2.5±3.6	2.2±4.1	**0.0002**[d]	0.71[d]

* p_{CC} = p case-control; p-value for comparison of characteristics between case subtypes and controls

§ p_{TH} = p tumour heterogeneity; p-value for comparison of characteristics between case subtypes

[a] One-way ANOVA

[b] Chi-square test

[c] Fisher's exact test

[d] Kruskal-Wallis test

6.2.1 ER/PR-defined Breast Tumours

Table 6.7 shows results for the polytomous logistic regression analysis of risk for ER/PR-defined breast tumour subgroups associated with leisure-time, household, and occupational MVPA across the life course among pre-menopausal women. Leisure-time and household MVPA were not associated with ER/PR+ or ER-/PR- breast cancer risk during any lifetime period, and no differences in odds ratios between tumour subgroups were observed. Breast cancer risk in the middle tertile of household MPVA during ages 18-34 was significantly different between ER/PR+ and ER-/PR- tumours (p for tumour heterogeneity, p_{TH} = 0.04), although individual ORs were not statistically significant. Occupational MVPA (3rd tertile vs. 0 MET-hrs/week) during ages 18-34 was associated with an over two-fold increase in ER/PR+ breast tumour risk (OR=2.07; 95% CI: 1.21, 3.55). An exposure-response relationship was observed between occupational MVPA during this time period and risk for ER/PR+ tumours (p_{trend}=0.06) but not ER-/PR- tumours (p_{trend}=0.26), although risks for tumour subtypes were not significantly different at any individual levels of occupational MVPA exposure (p_{TH} = 0.71).

Table 6.7 Adjusted ORs (95% CI) for the association between lifetime MVPA and risk for ER/PR-defined breast cancer by age period among pre-menopausal women

MVPA (mean MET-hrs/wk)	Controls (n=384)	ER+ and/or PR+ (n=277)		ER-/PR- (n=78)		p_{TH} [§]
		n (%)	OR (95% CI)[*]	n (%)	OR (95% CI)[*]	
Leisure-time						
12 – 17 years						
0 MET-hrs/wk	100 (26)	79 (29)	1.00 (reference)	23 (29)	1.00 (reference)	
≤12.1	93 (25)	62 (22)	0.95 (0.60, 1.51)	19 (24)	1.03 (0.51, 2.06)	0.77
12.11 – 33.0	94 (24)	70 (25)	1.34 (0.84, 2.13)	21 (27)	1.45 (0.72, 2.93)	0.75
>33.0	97 (25)	66 (24)	1.25 (0.78, 1.99)	15 (19)	1.03 (0.48, 2.19)	0.69
p trend			0.20		0.68	
18 – 34 years						
0 MET-hrs/wk	82 (21)	80 (29)	1.00 (reference)	23 (29)	1.00 (reference)	
≤8.1	99 (26)	88 (32)	1.14 (0.73, 1.80)	27 (35)	1.24 (0.63, 2.41)	0.59
8.11 – 24.1	100 (26)	58 (21)	0.75 (0.46, 1.23)	16 (21)	0.70 (0.33, 1.51)	0.88
>24.1	103 (27)	51 (18)	0.75 (0.45, 1.26)	12 (15)	0.63 (0.27, 1.44)	0.97
p trend			0.11		0.13	
35 – 49 years						
0 MET-hrs/wk	94 (24)	95 (34)	1.00 (reference)	26 (33)	1.00 (reference)	
≤10.3	95 (25)	79 (29)	1.01 (0.65, 1.56)	27 (35)	1.34 (0.71, 2.55)	0.29
10.31 – 28.9	96 (25)	55 (20)	0.79 (0.49, 1.26)	16 (21)	0.86 (0.42, 1.79)	0.79
>28.9	99 (26)	48 (17)	0.71 (0.43, 1.17)	9 (12)	0.53 (0.22, 1.26)	0.71
p trend			0.11		0.12	
Total Lifetime						
0 MET-hrs/wk	31 (8)	29 (10)	1.00 (reference)	12 (15)	1.00 (reference)	
≤10.9	115 (30)	119 (43)	1.27 (0.70, 2.31)	31 (40)	0.79 (0.35, 1.78)	0.26
10.91 – 25.3	117 (30)	60 (22)	0.73 (0.38, 1.38)	21 (27)	0.59 (0.24, 1.43)	0.65
>25.3	121 (31)	69 (25)	0.92 (0.48, 1.76)	14 (18)	0.45 (0.17, 1.17)	0.19
p trend			0.21		0.07	
Household						
12 – 17 years						
0 MET-hrs/wk	320 (83)	240 (87)	1.00 (reference)	65 (83)	1.00 (reference)	
≤8.0	21 (5.5)	13 (5)	0.94 (0.44, 1.98)	3 (4)	0.94 (0.26, 3.41)	0.94
8.01 – 44.3	21 (5.5)	15 (5)	1.20 (0.59, 2.44)	7 (9)	2.05 (0.80, 5.23)	0.28
>44.3	22 (6)	9 (3)	0.45 (0.20, 1.04)	9 (3)	0.60 (0.17, 2.14)	0.74
p trend			0.21		0.89	
18 – 34 years						
0 MET-hrs/wk	155 (40)	131 (47)	1.00 (reference)	31 (40)	1.00 (reference)	
≤9.5	75 (20)	41 (15)	0.73 (0.46, 1.18)	10 (13)	0.80 (0.36, 1.79)	0.70
9.51 – 66.5	74 (19)	45 (16)	0.76 (0.48, 1.23)	21 (27)	1.52 (0.77, 2.98)	**0.04**
>66.5	80 (21)	60 (22)	0.77 (0.48, 1.22)	16 (21)	0.80 (0.40, 1.65)	0.83
p trend			0.19		0.93	
35 – 49 years						
0 MET-hrs/wk	161 (42)	126 (45)	1.00 (reference)	34 (44)	1.00 (reference)	
≤16.3	73 (19)	48 (17)	0.98 (0.62, 1.53)	13 (17)	0.98 (0.48, 2.03)	0.77
16.31 – 103.6	74 (19)	47 (17)	0.88 (0.55, 1.39)	17 (22)	1.16 (0.58, 2.32)	0.34
>103.6	76 (20)	56 (20)	0.85 (0.53, 1.36)	14 (18)	0.72 (0.34, 1.52)	0.71
p trend			0.45		0.56	
Total Lifetime						
0 MET-hrs/wk	134 (35)	105 (38)	1.00 (reference)	24 (31)	1.00 (reference)	
≤26.0	82 (21)	50 (18)	0.97 (0.61, 1.54)	13 (17)	1.21 (0.56, 2.61)	0.51

26.01 – 86.6	83 (22)	58 (21)	0.94 (0.59, 1.50)	25 (32)	1.76 (0.88, 3.50)	0.05
>86.6	85 (22)	64 (23)	0.88 (0.55, 1.42)	16 (21)	0.91 (0.42, 1.96)	0.91
p trend			0.61		0.82	
Occupational						
18 – 34 years ‡						
0 MET-hrs/wk	203 (53)	127 (46)	1.00 (reference)	38 (49)	1.00 (reference)	
≤35.2	57 (15)	39 (14)	1.40 (0.86, 2.28)	13 (17)	1.48 (0.71, 3.11)	0.77
35.21 – 79.4	61 (16)	47 (17)	1.56 (0.94, 2.60)	9 (12)	0.95 (0.40, 2.26)	0.29
>79.4	63 (16)	64 (23)	**2.07 (1.21, 3.55)**	18 (23)	1.75 (0.78, 3.94)	0.71
p trend			**0.006**		0.26	
35-49 years ¶						
0 MET-hrs/wk	223 (58)	153 (55)	1.00 (reference)	43 (55)	1.00 (reference)	
≤64.0	54 (14)	35 (13)	0.64 (0.37, 1.09)	10 (13)	0.68 (0.29, 1.55)	0.93
64.1 – 129.0	53 (14)	33 (12)	0.60 (0.34, 1.06)	12 (15)	0.88 (0.38, 2.02)	0.48
>129.0	54 (14)	56 (20)	0.94 (0.55, 1.63)	13 (17)	0.90 (0.38, 2.10)	0.77
p trend			0.56		0.80	
Total Lifetime						
0 MET-hrs/wk	159 (41)	94 (34)	1.00 (reference)	26 (33)	1.00 (reference)	
≤26.0	74 (19)	47 (17)	1.25 (0.78, 1.99)	15 (19)	1.43 (0.69, 2.96)	0.57
26.01 – 86.6	74 (19)	64 (23)	1.41 (0.90, 2.20)	19 (24)	0.42 (0.72, 2.83)	0.92
>86.6	77 (20)	26 (72)	**1.69 (1.09, 2.62)**	18 (23)	1.52 (0.75, 3.06)	0.62
p trend			**0.02**		0.22	

* Adjusted for age, education, ethnicity, ever oral contraceptive use, number of live births, and other MVPA domains in table (within each time period)

§ p_{TH} = p for tumour heterogeneity from case-case logistic regression model comparing ER-/PR- vs. ER/PR+ with same covariates as the polytomous case-control regression model

‡ Additionally adjusted for occupational MVPA performed during ages 35-49

¶ Additionally adjusted for occupational MVPA performed during ages 18-34

6.2.2 ER/PR/HER2-defined Breast Tumours

Table 6.8 shows results for the polytomous logistic regression analysis of risk for ER/PR/HER2-defined breast tumour subgroups associated with MVPA by age period among pre-menopausal women. Leisure-time and household MVPA were not associated with any tumour subgroup at any lifetime period, and no differences were detected between tumour subtypes in a case-case analysis with ER/PR+/HER2- as the reference. Occupational MVPA during ages 18-34 was associated with a two-fold increase in risk for ER/PR+/HER2- tumours (OR=2.09; 95% CI: 1.19, 3.69). An exposure-response relationship was observed for occupational MVPA during this time period and ER/PR+/HER2- tumours (p_{trend}=0.01), although case-case analysis showed no differences between tumour subtypes at any individual levels of occupational MVPA exposure.

Table 6.8 Adjusted ORs (95% CI) for the association between lifetime MVPA and risk for ER/PR/HER2-defined breast cancer among pre-menopausal women												
MVPA (mean MET-hrs/week)	Controls (n=384)	**ER/PR+/HER2- (n=224)**		**ER/PR+/HER2+ (n=53)**			**ER-/PR-/HER2+ (n=17)**			**ER-/PR-/HER2- (n=61)**		
		n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	p_{TH} §	n (%)	OR (95% CI)*	p_{TH} §	n (%)	OR (95% CI)*	p_{TH} §
Leisure-time												
12-17 years												
0 MET-hrs/wk	100 (26)	58 (26)	1.00 (reference)	21 (40)	1.00 (reference)	-	6 (35)	1.00 (reference)	-	17 (28)	1.00 (reference)	-
≤12.1	93 (24)	54 (24)	1.14 (0.70, 1.87)	8 (15)	0.45 (0.18, 1.08)	0.05	6 (35)	1.28 (0.38, 4.27)	0.99	13 (21)	0.94 (0.42, 2.09)	0.78
12.11 – 33.0	94 (25)	57 (25)	1.51 (0.92, 2.48)	13 (25)	0.85 (0.38, 1.90)	0.22	1 (6)	0.25 (0.03, 2.28)	0.09	20 (33)	1.87 (0.88, 3.97)	0.47
>33.0	97 (25)	55 (25)	1.44 (0.87, 2.38)	11 (21)	0.73 (0.31, 1.69)	0.15	4 (24)	1.00 (0.25, 4.01)	0.54	11 (18)	1.02 (0.43, 2.42)	0.56
p trend			0.09		0.63			0.67			0.51	
18-34 years												
0 MET-hrs/wk	82 (21)	64 (29)	1.00 (reference)	16 (30)	1.00 (reference)	-	5 (29)	1.00 (reference)	-	18 (30)	1.00 (reference)	-
≤8.1	99 (26)	68 (30)	1.11 (0.69, 1.80)	20 (38)	1.26 (0.59, 2.69)	0.73	7 (41)	1.76 (0.49, 6.35)	0.49	20 (33)	1.13 (0.54, 2.36)	0.69
8.11 – 24.1	100 (26)	49 (22)	0.77 (0.46, 1.30)	9 (17)	0.67 (0.27, 1.70)	0.83	2 (12)	0.44 (0.08, 2.56)	0.50	14 (23)	0.77 (0.34, 1.76)	0.96
>24.1	103 (27)	43 (19)	0.77 (0.45, 1.34)	8 (15)	0.65 (0.24, 1.74)	0.67	3 (18)	0.80 (0.16, 4.00)	0.81	9 (15)	0.59 (0.23, 1.48)	0.84
p trend			0.17		0.22			0.41			0.18	
35-49 years												
0 MET-hrs/wk	94 (24)	78 (35)	1.00 (reference)	17 (32)	1.00 (reference)	-	4 (24)	1.00 (reference)	-	22 (36)	1.00 (reference)	-
≤10.3	95 (25)	65 (29)	0.98 (0.62, 1.55)	14 (26)	1.13 (0.51, 2.50)	0.59	8 (47)	2.89 (0.79, 10.51)	0.08	19 (31)	1.09 (0.54, 2.21)	0.56
10.31 – 28.9	96 (25)	41 (18)	0.70 (0.42, 1.16)	14 (26)	1.25 (0.55, 2.84)	0.24	3 (18)	1.24 (0.25, 6.12)	0.52	13 (21)	0.79 (0.36, 1.74)	0.68
>28.9	99 (26)	40 (18)	0.69 (0.41, 1.17)	8 (15)	0.79 (0.30, 2.09)	0.76	2 (12)	0.95 (0.15, 5.98)	0.66	7 (11)	0.46 (0.17, 1.19)	0.55
p trend			0.08		0.79			0.82			0.10	
Total Lifetime												
0 MET-hrs/wk	31 (8)	21 (9)	1.0 (reference)	8 (15)	1.0 (reference)	-	3 (18)	1.0 (reference)	-	9 (15)	1.0 (reference)	-
≤10.9	115 (30)	94 (42)	1.36 (0.71, 2.60)	25 (47)	1.06 (0.42, 2.66)	0.59	7 (41)	0.86 (0.20, 3.78)	0.53	24 (39)	0.78 (0.32, 1.91)	0.28
10.9 – 25.3	117 (30)	49 (22)	0.80 (0.40, 1.61)	11 (21)	0.55 (0.19, 1.60)	0.64	4 (24)	0.53 (0.10, 2.81)	0.59	17 (28)	0.61 (0.23, 1.63)	0.69
>25.3	121 (32)	60 (27)	1.08 (0.53, 2.18)	9 (17)	0.52 (0.17, 1.60)	0.19	3 (27)	0.45 (0.07, 2.71)	0.37	11 (18)	0.45 (0.16, 1.31)	0.16
p trend			0.48		0.09			0.28			0.11	
Household												
12-17 years												
0 MET-hrs/wk	320 (83)	194 (87)	1.00 (reference)	46 (87)	1.00 (reference)	-	13 (76)	1.00 (reference)	-	52 (85)	1.00 (reference)	-
≤8.0	21 (5.5)	10 (4)	0.86 (0.38, 1.94)	3 (6)	1.33 (0.36, 4.91)	0.63	1 (6)	1.94 (0.22, 17.40)	0.56	2 (3)	0.75 (0.16, 3.49)	0.84
8.01 – 44.3	21 (5.5)	13 (6)	1.30 (0.62, 2.74)	2 (4)	0.79 (0.17, 3.58)	0.52	2 (12)	3.08 (0.61, 15.60)	0.28	5 (8)	1.84 (0.64, 5.29)	0.57
>44.3	22 (6)	7 (3)	0.44 (0.18, 1.09)	2 (4)	0.51 (0.11, 2.37)	0.94	1 (6)	1.19 (0.14, 10.15)	0.23	2 (3)	0.48 (0.11, 2.19)	0.97
p trend			0.26		0.45			0.37			0.81	
18-34 years												
0 MET-hrs/wk	155 (40)	106 (47)	1.00 (reference)	25 (47)	1.00 (reference)	-	8 (47)	1.00 (reference)	-	23 (38)	1.00 (reference)	-
≤9.5	75 (20)	34 (15)	0.73 (0.44, 1.21)	7 (13)	0.73 (0.29, 1.84)	0.87	1 (6)	0.30 (0.04, 2.53)	0.49	9 (15)	0.98 (0.42, 2.31)	0.42

9.51 – 66.5	74 (19)	38 (17)	0.79 (0.48, 1.30)	7 (13)	0.68 (0.27, 1.74)	0.86	6 (35)	1.94 (0.58, 6.44)	0.08	15 (25)	1.43 (0.67, 3.08)	0.11
>66.5	80 (21)	46 (21)	0.75 (0.46, 1.22)	14 (26)	0.82 (0.37, 1.81)	0.78	2 (12)	0.34 (0.07, 1.78)	0.38	14 (23)	0.97 (0.44, 2.14)	0.46
p trend			0.21		0.54			0.54			0.82	
35-49 years												
0 MET-hrs/wk	161 (42)	99 (44)	1.00 (reference)	27 (51)	1.00 (reference)	-	9 (53)	1.00 (reference)	-	25 (41)	1.00 (reference)	-
≤16.3	73 (19)	41 (18)	1.07 (0.66, 1.72)	7 (13)	0.66 (0.27, 1.63)	0.59	2 (12)	0.52 (0.11, 2.57)	0.54	11 (18)	1.16 (0.53, 2.55)	0.64
16.31 – 103.6	74 (19)	41 (18)	0.97 (0.60, 1.58)	6 (11)	0.55 (0.21, 1.46)	0.30	4 (24)	0.93 (0.25, 3.42)	0.84	13 (21)	1.24 (0.57, 2.68)	0.37
>103.6	75 (20)	43 (19)	0.85 (0.51, 1.41)	13 (25)	0.85 (0.38, 1.90)	0.92	2 (12)	0.35 (0.07, 1.81)	0.26	12 (20)	0.86 (0.38, 1.95)	0.80
p trend			0.56		0.50			0.28			0.89	
Total Lifetime												
0 MET-hrs/wk	134 (35)	82 (37)	1.0 (reference)	23 (43)	1.0 (reference)	-	6 (35)	1.0 (reference)	-	18 (30)	1.0 (reference)	-
≤13.2	82 (21)	41 (18)	0.98 (0.60, 1.61)	9 (17)	0.93 (0.39, 2.22)	0.96	3 (18)	1.14 (0.26, 5.01)	0.74	10 (17)	1.25 (0.53, 2.97)	0.55
13.21 – 62.0	83 (22)	54 (24)	1.11 (0.68, 1.79)	4 (8)	0.32 (0.10, 1.00)	0.05	5 (29)	1.66 (0.47, 5.86)	0.71	20 (33)	1.91 (0.89, 4.09)	0.11
>62.0	85 (22)	47 (21)	0.83 (0.50, 1.39)	17 (32)	1.02 (0.46, 2.25)	0.64	3 (18)	0.75 (0.17, 2.35)	0.63	13 (21)	1.04 (0.44, 2.45)	0.57
p trend			0.65		0.70			0.63			0.61	
Occupational												
18-34 years [‡]												
0 MET-hrs/wk	203 (53)	102 (46)	1.00 (reference)	25 (47)	1.00 (reference)	-	8 (47)	1.00 (reference)	-	30 (49)	1.00 (reference)	-
≤35.2	57 (15)	31 (14)	1.37 (0.81, 2.32)	8 (15)	1.45 (0.60, 3.53)	0.90	3 (18)	1.65 (0.39, 7.07)	0.82	10 (16)	1.47 (0.65, 3.33)	0.73
35.21 – 79.4	61 (16)	35 (16)	1.41 (0.81, 2.45)	12 (23)	2.16 (0.93, 5.04)	0.50	1 (6)	0.46 (0.05, 4.29)	0.40	8 (13)	1.12 (0.44, 2.81)	0.62
>79.4	63 (16)	56 (25)	**2.09 (1.19, 3.69)**	8 (15)	1.70 (0.61, 4.71)	0.54	5 (29)	1.89 (0.43, 8.36)	0.90	13 (21)	1.72 (0.69, 4.25)	0.68
p trend			**0.01**		0.12			0.55			0.29	
35-49 years [¶]												
0 MET-hrs/wk	223 (58)	120 (54)	1.00 (reference)	33 (63)	1.00 (reference)	-	8 (47)	1.00 (reference)	-	35 (57)	1.00 (reference)	-
≤64.0	54 (14)	26 (12)	0.63 (0.35, 1.12)	9 (17)	0.68 (0.28, 1.68)	0.80	3 (18)	1.20 (0.27, 5.41)	0.66	7 (11)	0.57 (0.21, 1.48)	0.60
64.01 – 129.0	53 (14)	28 (13)	0.66 (0.37, 1.22)	5 (9)	0.41 (0.14, 1.21)	0.50	3 (18)	1.38 (0.36, 7.23)	0.29	9 (15)	0.77 (0.31, 1.96)	0.60
>129.0	54 (14)	50 (22)	1.10 (0.62, 1.94)	6 (11)	0.46 (0.16, 1.33)	0.47	3 (18)	1.21 (0.22, 6.63)	0.68	10 (16)	0.84 (0.33, 2.13)	0.67
p trend			0.95		0.08			0.82			0.68	
Total Lifetime												
0 MET-hrs/wk	159 (41)	73 (33)	1.0 (reference)	21 (40)	1.0 (reference)	-	4 (24)	1.0 (reference)	-	22 (36)	1.0 (reference)	-
≤26.3	74 (19)	40 (18)	1.39 (0.84, 2.28)	7 (13)	0.81 (0.32, 2.05)	0.33	4 (24)	2.35 (0.55, 10.06)	0.52	11 (18)	1.24 (0.55, 2.78)	0.96
26.31 – 86.8	74 (19)	50 (22)	1.46 (0.90, 2.35)	14 (26)	1.25 (0.58, 2.68)	0.62	4 (24)	1.94 (0.45, 8.33)	0.76	15 (25)	1.31 (0.62, 2.75)	0.65
>86.8	77 (20)	61 (27)	**1.88 (1.18, 3.00)**	11 (21)	1.01 (0.44, 2.33)	0.13	5 (29)	2.70 (0.66, 11.09)	0.66	13 (21)	1.29 (0.59, 2.81)	0.23
p trend			**0.008**		0.77			0.19			0.46	

[*] Adjusted for age, ethnicity, education, ever oral contraceptive use, number of live births, other domains of MVPA in table (within each time period).

[§] p_{TH} = p for tumour heterogeneity from case-case logistic regression model comparing ER-/PR- vs. ER/PR+ with same covariates as the polytomous case-control regression model

[‡] Additionally adjusted for occupational MVPA during ages 35-49 years

[¶] Additionally adjusted for occupational MVPA during ages 18-34 years

Chapter 7

Discussion

7.1 Summary of Main Findings

7.1.1 Objective 1

This objective described leisure-time, household, and occupational MVPA across the life course for pre- and post-menopausal women and presented bivariate comparisons. Among pre- and post-menopausal women, cases and controls were more physically active during leisure-time as adolescents than as adults. Controls had higher mean MET-hrs/week of leisure-time MVPA than cases across all lifetime periods examined, with the exception of adolescence among pre-menopausal women, where no difference was observed. Most cases and controls did not engage in household MVPA as adolescents. No difference in mean MET-hrs/week of household MVPA was observed between pre-menopausal cases and controls at any lifetime period. Among post-menopausal women, controls performed more household activity per week on average than cases. Cases performed more occupational MVPA on average than controls among pre- and post-menopausal women, although differences were not statistically significant.

7.1.2 Objective 2

This objective investigated the independent effects of lifetime leisure-time, household, and occupational MVPA cumulatively and over four age periods of exposure on risk of pre- and post-menopausal women.

Among post-menopausal women, the highest levels of lifetime leisure-time and household MVPA were associated with breast cancer risk reductions of approximately 50%. Risk

reductions were observed for leisure-time and household MVPA in each age period across the life course, with the strongest reductions observed for adulthood. Among pre-menopausal women only, leisure-time MVPA performed during adulthood suggested slight reductions in risk of breast cancer, while no effect was observed for household MVPA at any age period across the life course. Occupational MVPA performed between ages 18-34 was associated with a doubling in pre-menopausal breast cancer risk and when performed at ages ≥50 was associated with a 60% increase in post-menopausal breast cancer risk.

Our findings for leisure-time and household MVPA are consistent with the general consensus that MVPA reduces risk for breast cancer (1,2). Studies similar to ours also indicate that physical activity over the total lifetime and later in life among post-menopausal women are particularly important for risk reduction (3-5). An important piece of our findings is the weekly MVPA energy expenditure dose at which we detected risk reductions for breast cancer: this result is relevant for development of strategies to improve physical activity levels among women for breast cancer prevention. The risk reduction of 50% observed with total lifetime leisure-time MVPA occurred only at the highest activity tertile of >24.9 MET-hrs per week. This volume is equivalent to running for 3 hours per week or accumulating 7.5 hours of brisk walking during the week. By comparison, the current Canadian physical activity guidelines for adults recommend 150 min per week of MVPA (6), approximately equivalent to 8.3 MET-hrs: three times lower than the 24.9 MET-hrs/week cut-off we observed. This disparity warrants further investigation.

Our results for occupational MVPA conflict with previous research indicating either null or protective effects among pre- and post-menopausal women (3-5,7-9). Two studies have reported increases in breast cancer risk associated with jobs involving moderate or heavy energy

expenditure (10,11). The first, designed to address high cancer incidence in Cape Cod, Massachusetts, found a 70% increase in risk associated with spending 10+ years in a medium/heavy physical job (10). The second, using National Cancer Institute job exposure matrix, found an increase in risk among post- but not pre-menopausal women, attributing it industrial exposures encountered by women in their study population who worked in factories during World War II (11). Similarly, our result may be attributed to confounding by occupational breast cancer risk factors associated with moderate and vigourous intensity jobs. The effect modification by age period we observed among pre-menopausal women, whereby a doubling in risk was associated with occupational MVPA during ages 18-34 and no effect was observed for ages 35-49, is of particular interest for further analyses.

In summary, results from objective two support the importance of leisure-time MVPA for reduction in breast cancer risk among post-menopausal women, particularly when performed later in life, and highlight the importance of active household work. No such effect was observed among pre-menopausal women. Increased pre-menopausal breast cancer risk associated with occupational MVPA performed during ages 18-34 requires investigation outside of this thesis. The weekly leisure-time MVPA energy expenditure dose associated with reduced post-menopausal breast cancer risk is over three times higher than what is recommended in current public health guidelines for physical activity, a disparity requiring further investigation.

7.1.3 Objective 3

This objective investigated the independent effects of lifetime leisure-time, household, and occupational MVPA cumulatively and over four age periods of exposure on ER/PR-defined and ER/PR/HER2-defined breast tumour subtypes among pre- and post-menopausal women.

Among post-menopausal women, the highest level of lifetime leisure-time MVPA was associated with a 40% reduction in risk for ER/PR+ breast tumours and a 70% reduction in risk for ER-/PR- tumours. Risk reductions were observed for MVPA in each age period, although the strongest reductions were associated with age periods 35-49 and ≥50 years for both tumour subgroups. When further stratified by HER2 tumour status, these effects appeared confined to HER2- tumour subtypes, although a case-case analysis showed no difference between tumour subtypes. Household MVPA across all adulthood age periods was associated with reduced risk for ER/PR+ breast tumours in an exposure-response fashion and this was not detected for ER-/PR- tumours, although case-case analysis showed no difference between tumour subtypes. When further stratified by HER2 status, household MVPA performed at ages ≥50 was associated with a greater risk reduction for ER/PR+/HER2- tumours than for ER/PR+/HER2+ tumours. Occupational MVPA performed at ages ≥50 was associated with an over two-fold increase risk for ER-/PR- and ER-/PR-/HER2 tumour subtypes.

Our results with respect to ER/PR-defined breast cancers among post-menopausal women are comparable with two studies examining leisure-time, household, and occupational MVPA by age period across the life course in relation to these tumour subtypes, finding no evidence for tumour heterogeneity across activity domains and lifetime periods (7,12). Other studies examining physical activity and ER/PR tumour status have examined recreational (13-18) or baseline (19) activity only, resulting in loss of exposure information. With respect to ER/PR/HER2-defined breast cancers, our results build on those of two previous studies, which examined recreational activity or leisure-time activity only at narrow time frames of exposure (20,21). Our results are difficult to consider with these two studies, as each compared two

subtypes while our study compared four. Nonetheless, our study and the two others observed risk reductions for breast tumour subtypes with MVPA (20,21). Our findings suggest the protective effects conferred by leisure-time MVPA may be restricted to HER2- tumour subtypes, although further evidence from larger studies is required to corroborate these results.

Among pre-menopausal women, leisure-time and household MVPA across the life course were not associated with risks of ER/PR-defined and ER/PR/HER2-defined breast tumours. Occupational MVPA performed during ages 18-34 was associated with over two-fold increases in risks of ER/PR+ and ER/PR+/HER2- breast tumour subtypes in exposure-response fashions that were not observed for other tumour subtypes, although case-case analysis showed no differences between subtypes. However, the analysis among pre-menopausal women is limited by lack of statistical power and we may have missed detecting any associations. No other study has examined leisure-time, household, or occupational MVPA across the life course in relation to ER/PR/HER2-defined breast cancer among pre-menopausal women.

In summary, objective 3 of thesis research found that MVPA across the life course reduces risk for post-menopausal breast cancer regardless of ER/PR and ER/PR/HER2 tumour status. We observed some notable differences: risk reductions associated with leisure-time MVPA appeared restricted to HER2- tumour subtypes; household MVPA during adulthood reduced risk for ER/PR+, ER/PR+/HER2-, and ER/PR+/HER2+ tumour subtypes but not others; and occupational MVPA during ages ≥50 increased risk for ER-/PR- and ER-/PR-/HER2- tumour subtypes. However, case-case analyses showed no differences between tumour subtypes, as the differences may have been too small to detect within our sample size.

7.2 Strengths and Limitations

Strengths of this thesis research include the large sample size of the MEBC study, the ability to include several potential confounders, the separate examination of menopausal groups, and comprehensive lifetime physical activity exposure assessment. Specifically, this research investigated leisure-time, household, and occupational MVPA independently by age period across the life course. The physical activity questionnaire used in this study is reliable, with test-retest Pearson's correlation coefficients of 0.72, 0.77, and 0.87 calculated for lifetime leisure-time, household, and occupational activity, respectively, in a study population similar to ours (22). MET scoring is a widely used measure that simultaneously captures volume and intensity, and is useful for relative comparisons of physical activity within study populations (23).

This research has some limitations. Although a comprehensive set of potential confounders was assessed in this study, we were unable to examine dietary factors, as they were not included in the study questionnaire. Diets high in saturated fat are a risk factor for breast cancer (24), and diet quality is associated with physical activity (25). However, the three studies most similar to ours reported that dietary factors did not confound the relationship between physical activity and breast cancer (3-5).

As a positive health behaviour, physical activity is most commonly over-reported when assessed by questionnaire (26,27). If physical activity over-reporting occurred and was non-differential between cases and controls, our results would underestimate the true effects of MVPA on breast cancer risk and overestimate energy expenditure doses where we observed protective effects. Reassuringly, the questionnaire used in this study is associated with better

reliability statistics for habitual activity and for bouts of moderate and vigourous intensity activities, the focus of this study, than for sporadic and light intensity activities (22).

If physical activity reporting (whether over-reporting or not) was differential between cases and controls, recall bias may have occurred. In this study, recall bias is most likely if cases concluded that they developed breast cancer due to being physically inactive and subsequently either under-reported physical activity, or, did not over-report while controls did so. However, the protective effects of physical activity against breast cancer were less well known at the time of study recruitment than they are now. In addition, stronger, well-known risk factors for breast cancer such as family history, pregnancy, and hormonal factors were also included in the study questionnaire, and consequently, any potential recall bias is more likely to have occurred with those factors than with physical activity. We thus expect than non-differential recall error is more likely to have occurred than recall bias with respect to physical activity in this study. If recall bias occurred, our results would overestimate the true effect of MVPA on breast cancer risk, although determination of the extent of bias would be difficult.

A central concern with potential selection bias for this study is that because cases were recruited from a population-based cancer registry and controls were recruited from a mammographic screening population, some cases would not have been eligible to be controls had they not developed breast cancer. A smaller proportion of controls than cases in this study belonged to an ethnic minority and achieved a high school education, although these differential characteristics and others were controlled for in statistical analysis. Sensitivity analyses were performed excluding all cases unlikely to have undergone routine mammographic screening, and results were unchanged from original analyses. Further, relatively low response

rates of 54% for cases and 57% for controls have potential to introduce response bias. However, because these rates were similar between cases and controls and there is no reason to expect that response was related to physical activity, the effect of this bias on results is likely minimal.

The distribution of breast tumour subtypes within cases in this study reflects that observed in other case groups, indicating that participation among cases was non-differential by breast tumour subtype. The Breast Cancer Association Consortium meta-analysis of 35,568 breast cancer cases from 34 studies observed 79% of breast tumours to be ER+ and/or PR+ and 21% to be ER-/PR- (28). In our study, 78% of both pre- and post-menopausal cases were ER+ and/or PR+ and 22% were ER-/PR-. In the meta-analysis, 67% of cases were ER+ and/or PR+/HER2-, 12% were ER+ and/or PR+/HER2+, 7% were ER-/PR-/HER2+, and 14% were ER-/PR-/HER2- (28). In our study, 65% of post-menopausal cases were ER+ and/or PR+/HER2-, 13% were ER+ and/or PR+/HER2+, 5% were ER-/PR-/HER2+, and 19% were ER-/PR-/HER2-. Corresponding percentages among pre-menopausal women were similar to these figures.

Although the large sample size of the MEBC study allowed stratification of the study population by menopausal status and by breast tumour subtype, this research lacks the ability to detect small differences in odds ratios and associated 95% confidence intervals within breast tumour subtypes and between certain subtypes and controls. Among pre-menopausal women, this limitation was so severe that it resulted in exclusion of results from the manuscript for publication. Among post-menopausal women, small numbers were observed in particular for ER+ and/or PR+/HER2+ (n=78) and ER-/PR-/HER2+ (n=31) tumours, as these are the two most rare subtypes. Linear trend tests that assessed exposure-response relationships overcame these sample size limitations to a certain degree. These tests indicated relationships with MVPA for

some tumour subtypes not observed with others, although we lacked statistical power to detect differences between tumour subtypes at individual levels of exposure in case-case analyses.

Despite the sample size limitation, the research for objective 3 of this thesis is novel. This study is the first to examine leisure-time, household, and occupational MVPA by age period across the life course on risk for these four breast tumour subtypes. Physical activity has never before been examined in relation to risk for the ER-/PR-/HER2+ breast tumour subtype.

7.3 Generalizability

Because this study population was comprised of women aged 40-80 years with no previous cancer history, results are not generalizable to women outside of this age group or with a cancer history. While the case group is reflective of the general population, approximately 53% of the eligible general population in the Vancouver Health Authority and 58-63% of the eligible general population in the Richmond Health Authority participated in the Screening Mammography Program between 2007 and 2010 and were eligible to be controls (29). Controls had higher educational attainment than cases and a higher proportion were of European ethnicity. These differences and others were controlled for in statistical analysis. Results were unchanged in sensitivity analyses removing cases unlikely to have participated in routine mammographic screening. The biology of the relationship between physical activity and breast cancer development is unlikely differential by ethnic group, as physical activity is shown to reduce breast cancer risk in Caucasian, Hispanic, Black and Asian populations (5,13,30,31). Given the distribution of ethnicities in our population, our results are likely generalizable to White and Asian Canadian women aged 40-80 years with no cancer history, who reside in urban centres similar to Vancouver.

7.4 Contribution of Research

This thesis research investigated the independent effects of leisure-time, household, and occupational MVPA across the life course on risk for overall breast cancer and ER/PR-defined and ER/PR/HER2-defined breast tumours while accounting for effect modification by menopausal status. This research supports the importance of leisure-time MVPA for prevention of post-menopausal breast cancer, particularly when performed later in life, and highlights the importance of active household work. Among post-menopausal women, leisure-time MVPA appeared to reduce risk regardless of ER/PR tumour status. However, the magnitude of protective effect of lifetime leisure-time MVPA was almost twice as strong for ER-/PR- tumours as ER/PR+ tumours. Whether this finding reflects a true biological difference conferred by MVPA on risk for the two tumour subtypes is uncertain and requires further investigation. We also found that the protective effects of leisure-time MVPA appeared restricted to HER2- tumours, another result requiring corroboration.

The results of this thesis support a causal role for MVPA in the development of breast cancer among post-menopausal women. These results are consistent with a body of evidence described as supportive of a "probable" causal relationship (32). Effect sizes were of strong magnitude for leisure-time and household MVPA, while effects of occupational MVPA are less strong or evident. The lifetime physical activity questionnaire utilized in this study allowed establishment of temporal sequencing. Breast cancer risk reductions were most strongly associated with MVPA performed later in life, which may represent the lifetime accumulation of protective hormonal, metabolic, and inflammatory effects of MVPA, since MVPA in early life was moderately positively correlated with activity later in life. MVPA performed after menopause

may be particularly important, as it protects against accumulation of hormonally active adipose tissue during this life period. Among pre-menopausal women, effects of MVPA are weaker and less certain both in this study and in previous literature (33).

With respect to leisure-time MVPA among post-menopausal women, the weekly MVPA energy expenditure dose associated with a decrease in breast cancer risk was over three times higher than current Canadian physical activity guidelines, which are intended to reduce risk for several chronic diseases including breast cancer. This finding raises the question of what is the most appropriate weekly dose of MVPA energy expenditure for breast cancer prevention, and whether current guidelines reflect this dose.

A recent nationally representative surveillance study that utilized objective measures of physical activity suggests that only 14% of Canadian women meet physical activity guidelines (34). Raising the guideline three-fold would likely result in an even lower proportion of the population who meet the guideline. Recognized barriers to participation in physical activity include time constraints, lack of motivation and self-efficacy, lack of personal and community resources, and lack of accessible sidewalks and green spaces (35). Neighbourhood socioeconomic status is a determinant of physical activity independent of individual socioeconomic status among women, which is partially explained by access to sidewalks, shops, and exercise facilities (36). The low proportion of the population meeting physical activity guidelines is particularly striking given this breadth of knowledge on barriers to physical activity. If physical activity guidelines were to be feasibly raised, sound individual- and structural-level strategies would need to be in place to allow the population to follow the guidelines – this achievement would require ongoing research, health promotion, healthy urban planning and

public policy. With further research on MVPA dose specific to breast cancer prevention, a more feasible intervention may be MVPA prescribed at a higher dose for women at risk for breast cancer, rather than for the general population.

An unexpected finding of this research is the increased breast cancer risk associated with occupational MVPA. Occupational MVPA during ages 18-34 was associated with a two-fold increase in risk ER/PR+ and ER/PR+/HER2- breast tumours among pre-menopausal women. Occupational MVPA during ages ≥50 was associated an over two-fold increase in risk for ER-/PR- and ER-/PR-/HER2- breast tumours among post-menopausal women. Previous research indicates that physically active jobs are beneficial to prevention of breast cancer, in addition to other chronic diseases (3,37-39). In fact, sedentary and inactive jobs are currently a main focus of research on negative health effects associated with work and physical activity (40, 41).

Further analysis of data from the MEBC study will attempt to explain the increase in breast cancer risk observed with occupational MVPA. This result is suspected to be a result of confounding by other occupational breast cancer risk factors associated with job intensity. While other graduate students using MEBC data are studying specific occupational exposures, job industries will be compared between women in the highest vs. lowest MVPA categories in an attempt to explain the observed risk increases associated with occupational MVPA.

7.5 Future Directions

An important public health question arising from this research is that of the minimum weekly MVPA energy expenditure dose required to prevent breast cancer. Findings from this thesis indicate this dose may be over three times higher than that recommended by current physical activity guidelines. The current guidelines were developed with a sound evidence base

from systematic reviews of effects on several chronic diseases, and reflect the cut-off where substantial health benefits occur in the most holistic fashion (6). The guidelines have not been evaluated in terms of whether they represent the weekly MVPA dose required to reduce breast cancer risk.

A further nuance to the above question is whether the intensity in which weekly MVPA dose is accumulated affects risk: the cut-off for risk reduction we observed of 24.9 MET-hrs/week may be accumulated, for example, through running for 3 hours per week or through accumulating 7.5 hours of brisk walking in a week. The former example represents a vigourous intensity activity performed for a shorter duration, while the latter example is a moderate intensity activity performed for a longer duration. Some evidence from the cardiovascular health literature shows that vigourous intensity activity has a greater impact on metabolic syndrome risk than an equivalent energy expenditure dose of moderate intensity activity (42). Whether the same effect occurs with respect to breast cancer risk is unknown, warranting investigation for improvement of physical activity recommendations for breast cancer prevention.

This research also raises several questions regarding heterogeneity of effects of MVPA by ER/PR-defined and ER/PR/HER2-defined breast tumour subtypes. Whether or not MVPA has differential effects on breast tumour subtypes likely relates to biological mechanisms of MVPA. Effects of MVPA on sex hormones are thought to reduce risk for ER and PR positive tumours, while metabolic and inflammatory effects of MVPA may affect breast tumours regardless of receptor status. These proposed biological mechanisms for the effects of MVPA are not independent of one another and the degree to which one or another mechanism may affect risk is unknown. Whether HER2 is implicated in any of these mechanisms, as our results suggest, is

unclear. Randomized exercise trials for the effects of MVPA on proposed biomarkers of breast cancer risk have been undertaken (43-45), although follow-up for ER/PR/HER2-defined breast cancer as an outcome would take several years.

Perhaps as this body of evidence increases, targeted MVPA interventions may be designed for women at high risk of breast cancer. For instance, a greater dose of MVPA may be prescribed for such high risk women than what would be prescribed for the general population. If MVPA is found to have differential effects on different breast tumour subtypes, then MVPA interventions may be developed for women known to be at risk for specific subtypes based on presence of other risk factors. For example, if further research corroborates our finding that MVPA during leisure-time reduces risk for HER2- tumour subtypes, then MVPA interventions can be tailored specifically toward women with risk factors such as BRCA1 gene mutations and African ancestry, which are risk factors for ER-/PR-/HER2- tumours (46).

7.6 Conclusions

MVPA is a behaviour women may participate in to lower their risk of breast cancer. Physical activity at all age periods in life reduces risk, and leisure-time activity after age 35 is particularly important. Despite ongoing health promotion campaigns and physical activity recommendations targeted at individual behaviour change, only 14% of Canadian women meet current physical activity guidelines (34). Increasing amounts of research are targeted toward understanding individual and environmental determinants of participation in physical activity and will help improve support for physical activity participation in daily life. Further research on specific aspects of weekly MVPA energy expenditure dose required to reduce breast cancer risk will aid in refining physical activity recommendations for breast cancer prevention.

MVPA may be associated with reduced risk for ER/PR-defined and ER/PR/HER2-defined breast tumour subtypes at differing degrees; although, as the current body of knowledge stands, the overall message of physical activity for breast cancer prevention should be emphasized. Further research on etiologic heterogeneity of breast tumour subtypes in larger studies and in biomarker trials will help elucidate the biological mechanisms whereby MVPA reduces breast cancer risk. Understanding of the biological mechanisms whereby MVPA reduces breast cancer risk will advance knowledge of breast carcinogenesis and its prevention, and aid in development of MVPA interventions targeting breast cancer prevention.

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Appendix A
Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
June 21, 2011

Miss Lindsay Kobayashi
Department of Community Health and Epidemiology
Division of Cancer Care and Epidemiology,
Queen's Cancer Research Institute,
10 Stuart St. Level 2 Room 210,
Queen's University, Kingston, ON, K7L 3N6

Dear Dr. Kobayashi
Study Title: EPID-346-11 Physical activity across the life course and breast cancer risk
File # 6006052
Co-Investigators: Dr. Kristan Aronson

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol (May 2011) for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal FormÂ associated with your post review file # **6006052** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6006052** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

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

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

Yours sincerely,

Alison L. Clark

Chair, Research Ethics Board
June 21, 2011

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

Appendix B

MEBC Study Questionnaire

STUDY OF ENVIRONMENT, GENES AND BREAST HEALTH

RESEARCH QUESTIONNAIRE

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

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

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

We appreciate your cooperation tremendously.

Thank you!

GENERAL INFORMATION

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

Today's Date: _____
Month / day / year

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

2. What is the highest grade of school you have completed?
- Some elementary (grade) school
- Completed elementary (grade) school
- Some secondary (high) school
- Completed secondary (high) school
- Trade certificate (apprenticeship training)
- Certificate or diploma from a community college or CEGEP
- University degree (bachelor's degree)
- Graduate or professional school degree (above bachelor's degree)

3. What is your current employment status?
- employed (full-time)
- employed (part-time)
- self-employed (full-time)
- self-employed (part-time)
- homemaker
- student
- retired
- unemployed

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

GENERAL INFORMATION (Cont'd)

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

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

HEALTH AND MEDICAL BACKGROUND

6. What is your height? (feet and inches) or (cm)
7. What is your current weight? (lbs) or (kg)
8. a) What was your weight 2 years ago? (lbs) or (kg)
   b) What was your weight when you were 25 years old? (lbs) or (kg)
9. Not including pregnancy, what is the most you have weighed? (lbs) or (kg)
10. How old were you when you had your first menstrual period? years of age
    □ Have never menstruated (go to question #13)
11. Are you still menstruating?
    □ Yes (go to question #14)
    □ No
    ↓
    How many months or years has it been since your last menstrual period?
    _____ month(s)
    _____ years(s)
12. How did your menstrual periods stop?
    □ Naturally (through onset of menopause)
    □ As a result of a hysterectomy
    □ As a result of radiation or chemotherapy
    □ Other – please specify: _____

13. Have you ever had a hysterectomy (that is, an operation to remove the womb/uterus)?
    □ No
    □ Yes - at what age? years
14. Have you ever had an oopherectomy (that is, an operation to remove one or both of your ovaries which is sometimes done at the same time as removal of the womb/uterus)?
    □ No
    □ Yes, one ovary removed: → at what age? years
    □ Yes, second or both ovaries removed: → at what age? years
    □ Don't know
15. Have you ever had a tubal ligation (that is, sterilization by having your "tubes tied")?
    □ No
    □ Yes - at what age? Years

HEALTH AND MEDICAL BACKGROUND (Cont'd)

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

☐ No (go to question #17)

☐ Yes

↓

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

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

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

☐ No (go to question #18)

☐ Yes

↓

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

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

HEALTH AND MEDICAL BACKGROUND (Cont'd)

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

☐ No (go to question #19)

☐ Yes

↓

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

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

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

☐ No (go to question #20)

☐ Yes

↓

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

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

HEALTH AND MEDICAL BACKGROUND (Cont'd)

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

☐ Yes ☐ No (go to question# 22)

↓

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

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

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

☐ Yes ☐ No

The following questions are about screening for breast disease.

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

☐ Yes ☐ No (go to question #23)

↓

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

What was the reason?

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

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

23. Have you ever examined your own breasts for lumps?
□ Yes □ No (go to question #24)
↓
How old were you when you first started? _____ years
How often do you examine your breasts for lumps?
□ Weekly □ Monthly □ Quarterly (every 3 months) □ Yearly
□ Bi-weekly □ Bi-monthly □ Twice per year □ Unsure

HEALTH AND MEDICAL BACKGROUND (Cont'd)

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

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

PREGNANCY

25. Have you ever been pregnant? (include live births, still births, miscarriages and abortions)
□ Yes □ No (go to question #26)

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

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

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

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

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

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

FAMILY

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

The first five questions (#26 - #30) are about your:
- parents
- full brothers
- full sisters
- children.

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

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

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

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

26. How many full brothers do you have? _____

27. How many full sisters do you have? _____

28. How many children do you have? _____
    a. Number of sons? _____
    b. Number of daughters? _____

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

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

Full Brother 1		❑ Yes ❑ No ❑ Don't know			❑ Yes ❑ No ❑ Don't know		
Full Brother 2		❑ Yes ❑ No ❑ Don't know			❑ Yes ❑ No ❑ Don't know		
Son 1		❑ Yes ❑ No ❑ Don't know			❑ Yes ❑ No ❑ Don't know		
Son 2		❑ Yes ❑ No ❑ Don't know			❑ Yes ❑ No ❑ Don't know		
Daughter 1		❑ Yes ❑ No ❑ Don't know			❑ Yes ❑ No ❑ Don't know		
Daughter 2		❑ Yes ❑ No ❑ Don't know			❑ Yes ❑ No ❑ Don't know		

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

Are you aware of any such family members who have been diagnosed with cancer?

Yes ☐ No ☐

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

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

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

LIFESTYLE HABITS (TOBACCO and ALCOHOL)

32. Have you ever smoked more than 100 cigarettes in your lifetime?
□ Yes □ No (go to question #37)

33. How old were you when you STARTED smoking? _____ years of age

34. Are you currently smoking?
□ Yes □ No - If no, at what age did you quit? years

35. How many years in total have you smoked cigarettes? (excluding the years that you quit)
_____ years

36. For the entire time you smoked, on average, how many cigarettes a day did you usually smoke?
_____ cigarettes/day OR _____ cigarettes/week

37. This question asks about your family's smoking habits when you were 19 or younger.

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

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

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

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

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

41. This question asks about your alcohol consumption habits.

		Beer	Wine	Spirits
Have you ever drank the following more than twice a year? *(if "no" to all 3, i.e. beer, wine **and** spirits, go to question #41)*	Yes	❑	❑	❑
	No	❑	❑	❑

LIFESTYLE HABITS (PHYSICAL ACTIVITY - HOUSEHOLD)

The next question (#41) refers to the frequency, duration and intensity of household activities. The **minimum** number of hours for household activity to be included is:

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

Household activities (housework, yard work and home repair)

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

Light: Activities that require minimal physical effort such as:

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

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

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

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

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

LIFESTYLE HABITS (PHYSICAL ACTIVITY - HOUSEHOLD)

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

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

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

* Intensity of household activities defined as:

Light = activities that require minimal effort,

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

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

LIFESTYLE HABITS (PHYSICAL ACTIVITY – SPORTS AND EXERCISE)

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

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

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

The three categories of physical intensity level for exercise and sports activities are:
Light: Activities that require minimal physical effort such as those activities that are done standing or with slow walking
Moderate: Activities that are not exhausting, that increase the heart rate slightly and may cause some light perspiration
Heavy: Activities that increase the heart rate and cause heavy sweating.

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

An example of how to work with the table:
Activities:
from 8 yrs to 16 yrs played soccer- 1.5 hours per day, 2 days per week, 4 weeks per month, 4 months per year
from 25 yrs to 29 yrs played soccer - 2 hours per day, 2 days per week, 4 weeks per month, 8 months per year
from 18 to 49 played golf - 3 hours per day, 1 day per week, 4 weeks per month, 4 months per year

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

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

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

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

* Intensity of exercise/sports activity defined as:
Light = activities that require minimal effort,
Moderate = activities that are not exhausting, that increase the heart rate slightly and that may cause some light perspiration,
Heavy = activities that increase the heart rate and cause heavy sweating.

LIFESTYLE HABITS (SMOKED/GRILLED FOODS)

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

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

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

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

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

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

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

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

Congratulations!!

You are over halfway there!!

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

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

RESIDENTIAL HISTORY (GENERAL)

47. Please list the addresses in which you have lived for 1 year or more, throughout your lifetime, ending with your current address.

We understand that it may be difficult to recall detailed information for all residences throughout your lifetime and would appreciate it if you would enter as much information as you are able.

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

RESIDENTIAL HISTORY (GENERAL) (Cont'd)

47. (Cont'd)

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

RESIDENTIAL HISTORY (GENERAL) (Cont'd)

47. (Cont'd)

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

RESIDENTIAL HISTORY (GENERAL) (Cont'd)

47. (Cont'd)

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

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

RESIDENTIAL HISTORY (SOURCES OF ENERGY)

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

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

RESIDENTIAL HISTORY (SOURCES OF ENERGY)

48. (Cont'd)

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

RESIDENTIAL HISTORY (GENERAL ENVIRONMENT)

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

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

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

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

RESIDENTIAL HISTORY (INDOOR ENVIRONMENT)

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

Dark=could not see hand in front of face or wore a mask in bed Medium=could see to the end of the bed Light=could almost read without a light										
	1st Res	**2nd Res**	**3rd Res**	**4th Res**	**5th Res**	**6th Res**	**7th Res**	**8th Res**	**9th Res**	**10th Res**
Ambient light in bedroom at each residence	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑
If more than 10 residences, please continue:										
	11th Res	**12th Res**	**13th Res**	**14th Res**	**15th Res**	**16th Res**	**17th Res**	**18th Res**	**19th Res**	**20th Res**
Ambient light in bedroom at each residence	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑	Dark ❑ Med ❑ Light ❑

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

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

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

EMPLOYMENT HISTORY

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

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

* Intensity of job or occupation defined as:
Sedentary = work that involves sitting only, with minimal walking,
Light = work that involves minimal physical effort such as standing and slow walking with no increase in heart rate and no perspiration,
Moderate =work that is not exhausting, that increases the heart rate slightly and may cause some light perspiration, such as those that require carrying light loads (5-10 lbs) or that have continuous walking,
Heavy = work that is vigorous, increases the heart rate substantially and causes heavy sweating such as those that involve lifting, carrying heavy loads (>10 lbs), brisk walking, or climbing.

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

EMPLOYMENT HISTORY (Cont'd)

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

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

* Intensity of job or occupation defined as:

Sedentary = work that involves sitting only, with minimal walking,
Light = work that involves minimal physical effort such as standing and slow walking with no increase in heart rate and no perspiration,
Moderate =work that is not exhausting, that increases the heart rate slightly and may cause some light perspiration, such as those that require carrying light loads (5-10 lbs) or that have continuous walking,
Heavy = work that is vigorous, increases the heart rate substantially and causes heavy sweating such as those that involve lifting, carrying heavy loads (>10 lbs), brisk walking, or climbing.

EMPLOYMENT HISTORY (Cont'd)

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

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

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

EMPLOYMENT HISTORY (Cont'd)

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

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

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

EMPLOYMENT HISTORY (Cont'd)

54 (Cont'd)

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

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

EMPLOYMENT HISTORY (Cont'd)

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

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

EMPLOYMENT HISTORY (Cont'd)

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

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

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

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

INCOME

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

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

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

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

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

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

_____
_____
_____
_____

Appendix C

MET Score Legend

Household Activity

1. **Home Activities, light, MET=2.5:**

- Sweeping: 3.3
- Vacuuming: 3
- Dusting (cleaning, light): 2.5
- Cooking and food preparation standing or sitting: 2.0
- Putting away groceries: 2.5
- Shopping: 2.3
- Ironing: 2.3
- Laundry: 2.0
- Home activities, general (light): 2.5

2. **Home Activities, moderate, MET=2.5:**

- Food shopping with a grocery cart: 2.3
- Packing/unpacking boxes, occasional lifting of household items: 3.5
- Child care, light effort: 2.5
- Cleaning house, general: 3.0
  **Assigned MET score of 2.5 because the overwhelming majority of responses within this category were child care.

3. **Home Activities, heavy, MET=3.5:**

- Major cleaning (wash car, windows, mop, clean garage, sweeping sidewalk, scrubbing floors, moving large items): 3.0
- Child care, moderate to heavy effort: 4.0
- Animal care (moderate): 3.0

4. **Home Repair, light, MET=3.0:**

- Automobile repair: 3.0
- Wiring, plumbing: 3.0
- Carpentry, workshop: 3.0

5. **Home Repair, moderate, MET=4.5:**

- Automobile body work: 4.0
- Finishing/re-finishing cabinets or furniture: 4.5
- Caulking: 4.5
- Laying tile/carpet: 4.5
- Painting, papering, plastering, scraping: 3.0
- Sanding floors: 4.5
- Washing/waxing/painting a car or boat: 4.5
- Washing fence: 4.5
- Home repair, general (moderate): 4.5

6. **Home Repair, heavy, MET=5.5:**
- Outside carpentry, installing rain gutters: 6.0
- Roofing: 6.0
- Sawing hardwood: 7.5
- Spreading dirt with a shovel: 5.0
- Painting outside house: 5.0

7. **Lawn and Garden, light, MET=2.5:**
- Watering lawn: 1.5
- Fertilizing or seeding lawn: 2.5
- Standing or walking in garden: 3.0
- Mowing lawn on a rider mower: 2.5
- Yard work (light): 2.0

8. **Lawn and Garden, moderate, MET=4.5:**
- Mowing lawn with a power mower: 5.5
- Trimming shrubs/trees: 4.0
- Operating a snow blower: 4.5
- Planting seedlings/shrubs/trees: 4.5
- Weeding: 4.5
- General gardening: 4.0
- Sacking leaves/grass: 4.0
- Farm activities (moderate): 4.5
- Yard work (moderate): 3.0

9. **Lawn and Garden, heavy, MET=5.5:**
- Carrying/stacking wood/lumber: 5.0
- Chopping wood, splitting logs: 6.0
- Clearing land, hauling branches: 5.0
- Digging, spading, filling garden: 5.0
- Laying sod: 5.0
- Laying rock: 5.0
- Mowing lawn with a push mower: 6.0
- Shovelling snow by hand: 6.0

Occupational Activity

Moderate Intensity Job: MET=3.0
Vigourous Intensity Job: MET=6.0

Leisure-Time Activity

Look_PAexercise			
RAID	**RADesc**	**RACode**	**RAMet**
1	Aerobics, general	1	6.5
2	Aerobics, jazzercise, slimnastics	198	6.0
3	Aerobic dancing, low impact	2	5.0
4	Aerobic dancing, high impact	3	7.0
5	Aerobics, step (6-8")	196	8.5
6	Aerobics, step (10-12" step)	197	10.0
7	Animals, run/play moderate (not walk dog)	191	4.0
8	Aquacize, water calisthenics, treading water	160	4.0
9	Archery (non-hunting)	4	3.5
10	Backpacking	5	7.0
11	Badminton, general, social	6	4.5
12	Badminton, competitive	7	7.0
13	Basketball, game	8	8.0
14	Basketball, nongame, general	9	6.0
15	Basketball, shooting baskets	10	4.5
16	Basketball, wheelchair	11	6.5
17	Bicycling, light	12	6.0
18	Bicycling, moderate effort	13	8.0
19	Bicycling, vigorous effort	14	10
20	Bicycling, stationary, general	15	7.0
21	Bicycling, stationary, moderate effort	16	7.0
22	Bicycling, stationary, vigorous effort	17	10.5
23	Billiards	18	2.5
24	Boating, power	167	2.5
25	Bowling	19	3.0
26	Boxing, in ring, general	20	12
27	Boxing, punching bag	21	6.0
28	Boxing, sparring	22	9.0
29	Broomball	182	7.0
30	Calisthenics, heavy or vigorous (pushups, situps, jumping jacks)	24	8.0
31	Camping	189	2.5
32	Canoeing, rowing for pleasure, general	199	3.5
33	Canoeing, on camping trip	25	4.0
34	Canoeing, rowing, in competition, or crew or sculling	26	12
35	Children's games (hopscotch, dodgeball, t-ball, etc.)	27	5.0
36	Circuit training, general with aerobics & minimal rest	28	8.0
37	Coaching (soccer, basketball, baseball, swimming, etc.)	29	4.0
38	Cricket (batting, bowling)	30	5.0
39	Croquet	31	2.5
40	Curling	32	4.0
41	Dancing, general, (Greek, Middle Eastern, Flamenco, etc.)	33	4.5
42	Dancing, slow (ballroom dancing such as foxtrot, waltz)	34	3.0
43	Dancing, fast (disco, folk, square, Irish step, etc.)	35	4.5
44	Dancing, (ballet or modern, jazz, tap, jitterbug, etc.)	192	4.8

45	Darts, wall or lawn	36	2.5
46	Deepwater running/water jogging	161	8.0
47	Diving	37	3.0
48	Drag racing, pushing or driving a car	38	6.0
49	Fencing	39	6.0
50	Fishing, sitting (fishing from a boat)	40	2.5
51	Fishing, general	195	3.0
52	Fishing, standing (fishing standing from a riverbank)	41	3.5
53	Fishing, walking (fishing from a riverbank and walking)	42	4.0
54	Fishing, in stream (in waders)	43	6.0
55	Football, competitive	44	9.0
56	Football, touch, flag, general	45	8.0
57	Football/baseball, playing catch	46	2.5
58	Frisbee playing, general	47	3.0
59	Frisbee, ultimate	48	8.0
60	Golf, walking and carrying clubs, general	49	4.5
61	Golf, walking and pulling clubs	50	4.3
62	Golf, miniature, driving range	51	3.0
63	Golf, using power cart	53	3.5
64	Gymnastics, general	54	4.0
65	Gym classes, general	162	5.5
66	Hacky sack	188	4.0
67	Handball, general	55	12.0
68	Hang gliding	57	3.5
69	Health Club, exercise, general	58	5.5
70	Hiking, cross country	59	6.0
71	Hockey, field, hand	60	8.0
72	Hockey, floor	186	8.0
73	Hockey, ice	61	8.0
74	Horseback riding,	62	4.0
75	Horseback riding, trotting	63	6.5
76	Horseback riding, rodeo, galloping	64	8.0
77	Horseshoe pitching	180	3.0
78	Hunting, light effort (bow & arrows or crossbow, duck hunting, pistol shooting)	65	2.5
79	Hunting, moderate effort (rabbit, squirrel, prairie chicken, raccoon, small game, general hunting)	66	5.0
80	Hunting, heavy effort (pheasants, grouse, deer, elk, large game)	67	6.0
81	Jogging, general	68	7.0
82	Jogging/walking combination (jogging less than 10 minutes)	69	6.0
83	Judo, jujitsu, karate, kick boxing, tae kwon do	70	10
84	Kayaking	71	5.0
85	Kickball	72	7.0
86	Lacrosse	73	8.0
87	Moto-cross	74	4.0
88	Motor cycling	166	2.5
89	Orienteering	75	9.0

90	Paddleball, competitive	76	10
91	Paddleball, casual, general	77	6.0
92	Paddleboat	78	4.0
93	Polo	79	8.0
94	Quading	187	3.0
95	Racketball, competitive	80	10.0
96	Racketball, general, casual	81	7.0
97	Rock or mountain climbing	82	8.0
98	Rollerblading, in-line skating	183	12.5
99	Rope jumping, moderate, general	194	10.0
100	Rowing, stationary ergometer, glider, elliptical trainer, light effort	83	3.5
101	Rowing, stationary ergometer, glider, elliptical trainer, moderate effort	84	7.0
102	Rowing, stationary ergometer, glider, elliptical trainer, vigorous effort	85	8.5
103	Rugby	86	10.0
104	Running (12 minutes/mile)	87	8.0
105	Running (11.5 minutes/mile)	88	9.0
106	Running (10 minutes/mile)	89	10.0
107	Running (9 minutes/mile)	90	11.0
108	Running (8 minutes/mile)	91	12.5
109	Running (7 minutes/mile)	92	14.0
110	Running (6 minutes/mile)	93	16.0
111	Running, cross country	94	9.0
112	Running	95	8.0
113	Running, up stairs	96	15.0
114	Running on a track, team practice	97	10.0
115	Running, training, pushing a wheelchair	98	8.0
116	Sailing, boat and board sailing, windsurfing, ice sailing, general	100	3.0
117	Sailing, in competition	101	5.0
118	Scuba diving, general	102	7.0
119	Shuffleboard, lawn bowling	103	3.0
120	Skateboarding	104	5.0
121	Skating, ice (slow, less than 9 mph)	105	5.5
122	Skating, ice, moderate, general	106	7.0
123	Skating, ice (fast, >9 mph)	107	9.0
124	Skating, speed, competitive	108	15.0
125	Skating, roller or rollerblading, light or moderate	109	7.0
126	Skiing, general	110	7.0
127	Skiing, cross-country (slow or light effort, ski walking)	111	7.0
128	Skiing, cross country (moderate speed and effort)	112	8.0
129	Skiing, cross-country (vigorous effort, brisk speed)	113	9.0
130	Skiing, cross-country (racing)	114	14.0
131	Skiing, downhill (light effort)	115	5.0
132	Skiing, downhill or snowboarding (moderate effort)	116	6.0
133	Skiing, downhill (vigorous effort, racing)	117	8.0
134	Ski jumping (climb up/carry skis)	118	7.0
135	Ski machine, general (e.g., Nordic trainer)	119	7.0
136	Sky diving	120	3.5

137	Sledding, tobogganing, bobsledding, luge	121	7.0
138	Snorkeling	122	5.0
139	Snow shoeing	123	8.0
140	Snowmobiling	165	3.5
141	Soccer, competitive	124	10.0
142	Soccer, casual, general	125	7.0
143	Softball or baseball, fast or slow pitch, general	126	5.0
144	Softball, officiating	127	4.0
145	Softball, pitching	128	6.0
146	Squash	129	12.0
147	Stair ergometer, vigorous	130	9.0
148	Stretching mild, hatha, yoga, deep breathing	131	2.5
149	Surfing, body or board	132	3.0
150	Swimming, leisurely	133	6.0
151	Swimming, moderate	134	7.0
152	Swimming, vigorous effort	135	10.0
153	Swimming, synchronized, or water jogging,	193	8.0
154	Swimming, front crawl, fast (75 yds/min), vigorous effort or butterfly	136	11.0
155	Table tennis, ping pong	137	4.0
156	Tai Chi	181	4.0
157	Tennis, general	138	7.0
158	Tennis, doubles	139	6.0
159	Tennis, singles	140	8.0
160	Track and field, hammer throw, shot, discus	163	4.0
161	Track and field, high jump, long jump, triple jump, javelin, pole vault	184	6.0
162	Track and field, hurdles	185	10.0
163	Trampoline	141	3.5
164	Volleyball, competitive, in gym	142	8.0
165	Volleyball, non-competitive, 6-9 member team, general	143	3.0
166	Volleyball, beach	144	8.0
167	Walking, slow pace	145	2.5
168	Walking, moderate pace	146	3.3
169	Walking, brisk pace	147	3.8
170	Walking, uphill and carrying load 0-9 lbs	149	7.0
171	Walking, uphill and carrying load 10-20 lbs (4.5-9 kg)	150	7.5
172	Walking, uphill and carrying load 21-42 lbs (9.5-19 kg)	151	8.0
173	Walking, uphill and carrying load >42 lbs (20 kg)	152	9.0
174	Walking, upstairs	164	8.0
175	Water polo	153	10.0
176	Water volleyball	154	3.0
177	Water skiing	155	6.0
178	Weight lifting, light or moderate (free weights, nautilus or universal-type), light workout, general	156	3.0
179	Weight lifting, vigorous (free weights, nautilus or universal-type) power lifting or body building	157	6.0
180	Whitewater rafting, kayaking or canoeing	158	5.0
181	Wrestling	159	6.0

182	Teaching aerobics class	6.0
183	Calisthenics, home exercise, moderate or light effort	3.5
184	Walking the dog	3.0
185	Volleyball, general	4.0
186	Laundry	2.0
187	Standing, arts and crafts, vigourous effort (stone sculpting, pottery)	3.5
188	Standing, playing with children, active periods only, light (supervising children)	2.8
189	Bicycling, stationary, light effort	5.5
190	Meditating	1.0
191	Standing, light, moderate, assemble/repair heavy parts, auto repair, patient care/nursing, etc.	3.0
192	Bird watching (walking)	2.5
193	General gardening	4.0
194	Horse Grooming	6.0
195	Bicycling, BMX or mountain	8.5
196	Retreat/family reunion activities involving sitting, relaxing, talking, eating	1.5
197	Sitting – playing with child(ren) – light, only active periods	2.5
198	Walk/run – playing with child(ren) – moderate, only active periods	4.0
199	Walk/run – playing with child(ren) – vigourous, only active periods	5.0
200	Walk/run playing with animals, vigourous, only active periods	5.0
201	Moving furniture, household items, carrying boxes	6.0
202	Standing, singing in church, attending a ceremony, active participation	2.0
203	Cooking or food preparation – standing or sitting in general, manual appliances	2.0
204	Bicycling <10 mph, leisure, to work, or for pleasure	4.0
205	Whitewater rafting, kayaking, or canoeing	5.0
666	Other	
999	NA	

Appendix D

Example MET Score Calculations

Calculation for average MET-hrs/wk performed during one of the four age periods (12-17 years, 18-34 years, 35-49 years, and 50+ years) for a single participant:

MET-hrs/year of activity was calculated first. For each physical activity type reported, subjects recorded the age started and the age ended, the hours per day, days per week, weeks per month, and months per year the activity was performed.

MET-hrs/year = (hours per day)*(days per week)*(weeks per month)*(months per year)*(MET score of activity)

Mean MET-hrs/wk of activity performed over age period =
((# of years physical activity was performed within age period)*MET-hrs/year) / (# of weeks participant was alive during age period)

Hypothetical example:

A 55-year-old subject reports playing baseball from ages 45 to 55 for 3 hours per day, 2 days per week, 4 weeks per month, 4 months per year. The MET score for baseball is 5.0.

MET-hrs/year = (3)*(2)*(4)*(4)*(5.0) = 480

- Mean MET-hrs/wk of activity over **35-49 age period** =
  (5)*(480) / (780) = 3.08 MET-hrs/wk

- Mean MET-hrs/wk of activity over **50+ age period** =
  (6)*(480) / (312) = 9.23 MET-hrs/wk