

**LIFETIME PHYSICAL ACTIVITY AND THE RISK OF COLORECTAL CANCER:
A POPULATION-BASED CASE-CONTROL STUDY
USING DATA FROM THE NEWFOUNDLAND COLORECTAL CANCER REGISTRY**

By

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ABSTRACT

Although there is consistent evidence of an inverse association between physical activity and colorectal cancer (CRC), it is unclear whether physical activity has to be lifelong in order to protect against CRC, or whether there are critical time periods in which physical activity is most protective. This thesis investigated the association between recreational physical activities in specific age periods and across the lifetime and CRC risk in data from a population-based case control study (n=1395) in Newfoundland and Labrador. There were no significant associations between recreational physical activity at any age period or across the lifetime. Lack of association with activity in early adulthood is consistent with other studies in which this has been investigated. Lack of association in later life and across the lifetime may in part be explained by low levels of recreational physical activity, with only 30% of participants meeting World Cancer Research Fund cancer prevention recommendations.

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CHAPTER 1: INTRODUCTION

1. Background

Colorectal cancer (CRC) is the second most common cancer worldwide and the third most common cause of cancer death (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). It is estimated that one in fourteen males and one in sixteen females will develop CRC in their lifetime (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2014). There is considered to be 'convincing' evidence of an association between the overall risk of CRC and a family history of CRC, Crohn's disease and ulcerative colitis, physical activity, processed and red meat consumption, alcohol (in men and likely in women), tobacco smoking, total body fat, and abdominal fat (World Cancer Research Fund / American Institute for Cancer Research, 2007). Exposure to high levels of all of the above factors increases the risk of CRC, with the exception of physical activity where higher levels reduces the risk of CRC. There is accumulating evidence that diabetes also increases the risk of CRC (Sun & Yu, 2012) (Larsson, Orsini, & Wolk, 2005), and that calcium supplementation and aspirin use decrease the risk of CRC (World Cancer Research Fund / American Institute for Cancer Research, 2007). Several lines of evidence suggest lifestyle and dietary factors are central to CRC etiology. It is a reasonable hypothesis that changes in these habits aimed at reducing the risk of CRC may have a strong public health impact.

There are over 60 published epidemiological studies assessing the association between physical activity and colorectal cancer (CRC) (C. M. Friedenreich, Neilson, & Lynch, 2010). While most of these studies focused on recreational physical activity (also known as leisure-time physical activity), there is considerable variation between them in terms of timeframes in which activity was assessed, and the measurement instruments used. For these reasons, it is unclear

whether physical activity has to be lifelong in order to have protective effects, or whether there are critical time periods in which physical activity is most protective against CRC. Only 5 case-control studies have assessed associations between lifetime recreational physical activity and CRC (Boyle et al., 2011; Parent et al., 2010; Slattery, Edwards, & Ma, 1997; Steindorf et al., 2005). Majority of studies have collected information on recent physical activity: within 2 years prior to the CRC diagnosis for cases and prior to the date of interview for controls. However, there is substantial epidemiological evidence that CRC takes at least 10 years to develop in the general population (Morson, 1976; Spence, Heecsh, & Brown, 2009). It is unknown whether the effect of physical activity on CRC risk is differential by timing of its exposure throughout a person's lifetime. Thus, investigating the effect of physical activity at more than one point of time is potentially useful in furthering our understanding of CRC etiology. Studies that estimate physical activity at only one point in time (e.g., early adulthood) need to be interpreted with caution, particularly if the study did not control for physical activity performed at other time periods (Steindorf et al., 2005).

Lifetime occupation-related physical activity was assessed in some earlier studies, with most results suggesting an increased risk of colon cancer in people who had no or little activity from work-related tasks over their lifetime (Vena et al., 1985). However, occupational physical activity is not an attractive avenue for CRC prevention since most individuals do not have the choice in whether their occupations or work-related tasks include physical activity. In contrast, recreational activities may be performed by individuals of all ages and abilities during their leisure time, thus providing equal opportunity for all people to lower overall CRC risk. It should be noted that recreational forms of physical activity typically vary considerably in intensity, are

less regularly performed, and are of shorter duration when compared with occupational physical activity.

On the basis of systematic reviews, it has been concluded that there is convincing evidence of a significant inverse association between regular physical activity and the risk of developing CRC in men and women, independent of other lifestyle factors including obesity and diet (C. M. Friedenreich et al., 2010; Wolin, Yan, Colditz, & Lee, 2009; World Cancer Research Fund/American Institute for Cancer Research, 2011). Compared with those who are the least physically active, individuals who are most active have an estimated 30-40% reduction in their risk of CRC (Slattery, 2004). The reviews suggest that the role of physical activity in CRC risk may be the result of several biological mechanisms, notably improved insulin regulation (Giovannucci, 2003) and reduced central adiposity (C. M. Friedenreich et al., 2010). These reviews have been the basis of recommendations that a minimum of 30 minutes per day of moderate-to-vigorous intensity physical activity (>3.0 METs) performed on most days of the week may be needed to (significantly) reduce the risk of developing CRC among asymptomatic individuals (Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2010) (C. M. Friedenreich et al., 2010).

Investigating the association between lifetime physical activity and CRC should also address changes in physical activity participation over time. Patterns of change include: initiation, quitting, and replacing physical activity due to variety of physiological, environmental, and psychological factors such as changes in occupation, accessibility/the built environment, and/or health status. Assessing how different patterns of activity over time affect CRC risk may help guide appropriate and timely public health interventions.

Since most studies have been based on recent physical activity measures, there is insufficient evidence to suggest an optimal time period during the lifetime for engaging in physical activity to reduce the risk of developing CRC (Spence et al., 2009). In addition, most studies have not considered the effects of different types of physical activity (e.g., aerobic, anaerobic, or resistance training). These factors are potentially important components of a public health message aimed to reduce the risk of colon cancer through regular exercise, or physical activity.

Within Canada, mortality attributable to CRC is nearly twice as high in Newfoundland and Labrador compared to British Columbia, where CRC incidence and mortality rates are lowest (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). Newfoundland has the highest inherited component of risk yet reported worldwide (Green et al., 2007). Newfoundland also has among the lowest levels of physical activity levels in Canada (Gilmour, 2007). No study has examined the relationships between CRC and measures of physical activity in Newfoundland and Labrador.

2. Objectives

This thesis has two objectives. The primary objective is to investigate the association between recreational physical activities regularly performed in different periods of the lifecourse and CRC risk in Newfoundland, an area of high incidence of the disease. The secondary objective is to conduct a narrative review the literature on the associations between CRC and:

- a. lifetime cumulative recreational physical activity;
- b. recreational physical activity at different periods in the lifecourse.

3. Significance of Proposed Study

Colorectal cancer is thought to be one of the most preventable types of cancers, through healthy lifestyle choices (Slattery, 2004). One lifestyle modification that can reduce risk may be regular physical activity. Current national physical activity guidelines for the general population are intended to improve overall health and wellness. The latest guidelines from the Canadian Society for Exercise Physiology (CSEP) state that adults (18 years and older) should aim to get at least 150 minutes of moderate- to vigorous-intensity physical activity per week, in bouts of 10 min or more (Canadian Society for Exercise Physiology, 2012). It is stated that following these guidelines can reduce the risk of premature death, and a variety of chronic diseases including coronary heart disease, stroke, hypertension, and colon cancer (Canadian Society for Exercise Physiology, 2012). However, there is evidence to suggest that this may be inadequate for CRC prevention. The intensity and types of physical activity that need to be maintained at different periods during adult life to prevent CRC is not clear. If lifelong physical activity demonstrates the greatest risk reduction in CRC, then early intervention including physical education in elementary and high school may help initiate engagement with sports and increase the likelihood of a lifelong commitment to physical activity. This thesis has the potential to help guide future physical activity guidelines, by virtue of consideration of measures of physical activity in different timeframes and cumulatively during adult life.

4. Outline of Thesis

This thesis is composed of 5 chapters. The present chapter (Chapter 1) has provided background on the association between physical activity and CRC, identifying gaps in the evidence that lead to the rationale and objectives of the work. The next chapter (Chapter 2) provides definitions and presents methodological considerations, focussing on a detailed

description of the methods used to measure physical activity and their challenges. Chapter 2 also addresses the second objective of the thesis, by providing a review of studies that have investigated the association between CRC and physical activity across the lifetime or for more than 2 decades, and how this association may differ across subtypes of CRC. Chapters 3 and 4 address the primary objective of the thesis, documenting the methods and results of a population based case-control study examining lifetime physical activity and CRC using data from the Newfoundland Colorectal Cancer Registry (NFCCR) Study. Newfoundland has the highest rates of CRC in Canada, and one of the highest rates of familial CRC in the world (Green et al., 2007). It has been estimated that 90% of the current Newfoundland population has arisen from 20,000-30,000 original settlers (Green et al., 2007). As a result, they would have a high degree of kinship (genetic isolates with tight gene pool). No study has assessed lifetime physical activity and CRC in this population. It is unknown if moderate-vigorous activity is protective against CRC in this population. Finally, Chapter 5 provides a discussion of the findings of the analysis of the data from Newfoundland and Labrador, considering these in the broader context of the literature that has assessed lifetime physical activity, or physical activity during specific periods in the lifecourse.

CHAPTER 2: DEFINITIONS, METHODOLOGICAL CONSIDERATIONS, AND LITERATURE REVIEW OF LIFETIME PHYSICAL ACTIVITY AND CRC

1. Introduction

The epidemiological literature relating physical activity to colorectal cancer (CRC) risk includes more than 60 published studies. As there have been multiple systematic reviews, including the Continuous Update Project of the WCRF, it did not seem useful to undertake a new systematic review of this literature. Instead, the focus is on consideration of the associations between CRC and cumulative lifetime recreational activity, and activity during specific periods during the lifecourse. In addition, consideration is given to the possibility of differences in the magnitude of these associations by tumor subsite, noting that challenges exist in the classification of CRC, particularly relating to the separation of rectal cancer from cancer of the descending colon.

This Chapter begins with a general discussion of CRC epidemiology, followed by an overview of methods used to measure physical activity. Measuring physical activity in epidemiological research presents challenges, with a range of different methods previously employed. This chapter reviews the major methods which have been employed. The rest of the chapter focuses on two topics. First, we examine the evidence of lifetime physical activity and CRC risk, while highlighting the overall strengths and limitations. The focus on lifetime physical allows for integration of physical activity over the full exposure risk window. It also supports the analysis of physical activity within designated exposure windows across different ages. Secondly, the chapter summarizes the gaps in the literature regarding physical activity and CRC risk.

2. Overview of Colorectal Cancer Classification and Epidemiology

2.1. Descriptive Epidemiology of Colorectal Cancer

In Canada, the age-adjusted incidence rates for CRC were an estimated 60 cases per 100,000 for men and 40 cases per 100,000 for women in 2015 (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). CRC is the second most common cancer and cause of cancer death among men, and the third most common cancer and cause of cancer death in women (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). In Canada, CRC incidence rates for both men and women are highest in Newfoundland and Labrador (which also has the highest mortality rate of CRC for males and females), whereas the lowest rates for both sexes are in British Columbia (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015).

The observed geographic differences in CRC incidence observed within Canada and worldwide may be due to differences in modifiable risk factors and differences in availability of and participation in screening and diagnostic testing. A high incidence of CRC is consistently observed in populations with a Western diet (i.e., high caloric intake, foods rich in animal fat) combined with largely sedentary behavior. About two thirds of the incident cases occur in more developed countries, with the highest age-standardized rates (≥ 40 per 100,000 (in men)) occurring in Japan, Australia/New Zealand, North America, and western Europe, and lowest age-standardized rates occurring in parts of Africa, Central America, Melanesia, and South Central Asia (Little & Sharp, 2008). In recent years, there has been an increase in CRC in less developed countries and is now the 4th most common cancer in less developed countries (IARC, 2012). Geographic patterns are the same for women, but the rates are generally lower.

Moderate increases in CRC incidence have been observed in many populations over the last few decades, partially due to improvements in cancer detection and increases in screening participation. Generally, the increase in incidence has been more pronounced in men than women, or only observed in men (Little & Sharp, 2008). It wasn't until 2007 that the national Colorectal Cancer Screening network (nCCSn) was developed to increase attention to and focus on providing organized CRC screening to Canadians (Canadian Partnership Against Cancer, 2014). In Canada, 9 provincial organized screening programs were available as of 2014, and the remaining province has announced the intention to implement one. CRC screening programs across Canada have evolved at different rates (Canadian Partnership Against Cancer, 2014). For example, the Newfoundland and Labrador CRC Screening Program was just recently launched in 2012. Participation rates vary within and between the existing organized programs but most do not meet the target of 60% (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015).

2.2. Classification of colon and rectal cancer

Colorectal cancer develops in the colon (also known as the large intestine) and the rectum. The colon is divided into 4 major segments. The first segment is called the ascending colon; it begins with a pouch called the cecum, where undigested food is received from the small intestine, and extends upward on the right side of the abdomen (Drake, Vogl, & Mitchell, 2010). From that point, the colon crosses the body from the right to the left side and is called the transverse colon. The ascending and transverse segments are collectively referred to as the proximal colon. The third segment is the descending colon or distal colon, and extends downwards on the left side. The final part of the colon is the sigmoid colon. It is an "S" shape

and joins the rectum, which connects to the anus to expel digestive waste. The descending and sigmoid colon are referred to the distal colon (Drake et al., 2010).

The term colorectal cancer (CRC) commonly is used to refer to cancer occurring at any site in the colon or rectum. However, it can be used to refer to three distinct diseases: (1) cancer of the proximal colon; (2) cancer of the distal colon; and (3) cancer of the rectum (Quadrilatero & Hoffman-Goetz, 2003; Wei et al., 2003). Although they are close in proximity, the colon and rectum may serve different functions and are exposed to fecal matter for different lengths of time (Wei et al., 2003).

There is evidence of morphological, molecular, and epidemiological differences between proximal and distal colon cancer (Iacopetta, 2002). It has been suggested that the major forms of familial CRC may first form in different segments of the bowel: FAP first arising from the distal colon and rectum, and HNPCC first arising in the proximal colon (Iacopetta, 2002). Distal colon cancer and rectal cancer are more similar in terms of mutational frequencies than cancers of the proximal colon (Robsahm et al., 2013). Much of the epidemiological literature considers all sites of CRC as a single endpoint. This ignores the possibility that heterogeneity exists between the tumors at the three sites (Wei et al., 2003). If colon and rectal cancers have distinct aetiologies, it may be inappropriate to use CRC alone as an end-point in analyses (Wei et al., 2003).

2.3. The association between physical activity and distal and proximal colon cancer

The association between physical activity and CRC was examined in the Second Expert Report on Food, Nutrition, Physical Activity, and the Prevention of Cancer prepared by the World Cancer Research Foundation (WCRF) and the American Institute for Cancer Research (AICR) (World Cancer Research Fund / American Institute for Cancer Research, 2007). They

reported a strong and consistent inverse association between recreational, occupational, and total physical activity and CRC risk. Three systematic literature reviews (SRs) were published since that report and have confirmed these results (Huxley et al., 2009; Pham et al., 2012; Robsahm et al., 2013).

Among the two SRs that were based on cohort studies that have examined the colon as two distinct diseases (colon and rectal), results have shown a significant association between physical activity and proximal colon cancers (Robsahm et al., 2013; World Cancer Research Fund / American Institute for Cancer Research, 2007). Some case-control studies have also found a significant inverse association between proximal colon cancer and physical activity (C. Friedenreich et al., 2006) (Lee et al., 2007). To date, only two studies reported the effect of age period-specific physical activity on proximal and distal colon cancers separately (Boyle et al., 2011; Marcus, Newcomb, & Storer, 1994). One study assessed left and right colon cancers separately in early adulthood (14-22) in women and found no association with total physical activity (Marcus et al., 1994). The other study found a general trend towards greater risk reductions with each advancing age period in the association of physical activity and distal but not proximal colon cancer (Boyle et al., 2011). Only one study has assessed the association between lifetime physical activity and proximal and distal colon cancers separately (Boyle et al., 2011). Boyle et al., found a significant inverse association between vigorous physical activity performed consistently across the adult lifetime and distal colon cancer risk, but no association was found for proximal colon cancer risk. Based on the existing literature, there is conflicting evidence for a potential link of physical activity to the risk of distal colon cancer (World Cancer Research Fund/American Institute for Cancer Research, 2011).

Rectal cancer, examined as a separate entity, demonstrates a lack of an association with physical activity (World Cancer Research Fund/American Institute for Cancer Research, 2011)(Spence et al., 2009)(Pham et al., 2012). Studies of rectal cancer have often been limited by low statistical power because rectal cancers account for approximately ~30% of all large bowel cancer (Wei et al., 2003). As a result, many reports have stated that evidence for rectal cancer and physical activity is inconclusive (World Cancer Research Fund / American Institute for Cancer Research, 2007).

3. Overview of Issues in the Measurement of Leisure Time Physical Activity

The following section outlines the definition of physical activity and various measures of physical activity in the epidemiological literature. These approaches have been extensively reviewed in the IARC Cancer Prevention Handbook (2002) (International Agency for Research on Cancer, 2002) and were the basis of this review. We extend from these techniques and comment on their use in case-control studies specifically.

3.1 Definition of Physical Activity

Physical activity is defined as, ‘bodily movement produced by skeletal muscles resulting in a quantifiable form of energy expenditure’ (International Agency for Research on Cancer, 2002, page 6). Measurement of physical activity is complex and involves obtaining information on many components including:

- type of activity (i.e., occupational, recreational or leisure-time, household, and transportation);
- dose (frequency, intensity, duration);
- time period in life for when it was performed

Some of the inconsistencies found in the literature regarding physical activity and CRC may be attributed to differences in how these components are measured. Furthermore, some studies investigate exercise rather than physical activity as a whole. Exercise is defined as, ‘a regular and structured subset of physical activity performed deliberately and with a specific purpose’ (Shephard, 2003, page 197), such as preparing for an athletic event, or the improvement of fitness component. This distinction is important. The quantity and quality of exercise needed to attain health-related benefits may differ from what is recommended for fitness benefits (Garber et al., 2011). Likewise, initial level of fitness may impact the size of effect of physical activity on a number of health outcomes.

3.2 Measurement of physical activity

A critical component for epidemiological research is the accurate assessment of the exposure of interest (Laporte, Montoye, & Caspersen, 1985). Physical activity has been estimated using a variety of data collection methods including: self-reported questionnaires, diary surveys, behavior observation, calorimetry, and mechanical and electronic monitoring (e.g. pedometers and accelerometers), or a combination of these methods (Laporte et al., 1985). The fundamental issue is the inherent trade-off between practicality and validity. There has been very little standardization in the methods used for assessing physical activity and for measuring its association with cancer outcomes; hence, some of the heterogeneity in the literature may be attributable to the large variations in the measurement of the exposures (C. M. Friedenreich, 2001). Regardless of the method used, the accuracy of the measurement of the physical activity should be equivalent among cases and control (Wacholder, Silverman, McLaughlin, & Mandel, 1992). The different instruments that have been used in physical activity research will be

outlined with a brief discussion of their validity, reliability, and practicality. A comparison of their validity and reliability is summarized in Table 1.

Table 1. Summary of methods of measuring physical activity

	Examples	Validity (Spearman's Rho)	Reliability (ICC)	Practicality for lifetime measurement (Y/N)
Global Questionnaires	The global physical activity questionnaire (GPAQ)	0.40 to 0.59	0.43 to 0.81	N: typically limited to recent activity
Single-item questionnaires	The Godin questionnaire	0.19 to 0.40	2 to 4 week: 0.24-0.48 (light); 0.84-0.94 (vigorous)	N: limited to exercise over a 'typical week'
Comprehensive questionnaires	CARDIA questionnaire	0.84 (vigorous); 0.81 (total PA)	0.79	Y: long-term activity; 15-60 items
Quantitative histories	The Minnesota Leisure-time Physical Activity (MLTPA)	≥ 0.47	4 weeks = 0.80; 1 year = 0.71 for heavy activities	Y: detailed recall for time frames up to one year or longer; flexibility; but poor response rate
Motion sensors (e.g. pedometer/accelerometer)	Omron (OM) pedometer; FitBit (One, Zip)	OM = 0.69 waist-mounted sensor; 0.43 leg mounted; FitBit = 0.86 (mean bias -4.5 ± 1.0 kcals/6 min)	walking/running Fitbit interdevice steps 0.76–1.00, intraclass distance 0.90–0.99), energy expenditure 0.71–0.97	OM= N: typically limited to recent activity depending on device; Fitbit: Y, though no data on long-term data

References: (Slattery & Jacobs, 1995; Godin & Shephard, 1985; Albanes, Conway, Taylor, Moe, & Judd, 1990; Richardson, Leon, Jacobs, Ainsworth, & Serfass, 1994; Helmerhorst et al., 2012; Evenson et al., 2015).

3.2.1 Questionnaires

Questionnaires are among the most common methods of measuring physical activity because of practical considerations. However, they also allow for the collection of all of the physical activity parameters including: type of activities, intensity, duration and frequency. Questionnaires can vary greatly in their detail, the age period surveyed (up to and including the entire lifespan), and the method of administration (e.g., self- or interviewer-administered).

Questionnaires can be characterized as “global”, “single-item”, “comprehensive”, or “quantitative histories”. Among the questionnaires available, quantitative histories and comprehensive questionnaires offer the most detailed measurement of physical activity. For example, the comprehensive CARDIA questionnaire asked respondents to recall the number of months they performed an activity for one hour, and two hours in the last 12 months using 13 activity categories (Slattery & Jacobs, 1995). Quantitative histories provide the most thorough assessment of physical activity using a questionnaire approach, because they required detailed recall for time frames up to one year or longer (International Agency for Research on Cancer, 2002). Due to its extensive time to administer, it is the most expensive of the questionnaires, and often is limited by poor response rates. This type of questionnaire offers great flexibility, and permits the assessment of seasonal physical activities, which is particularly relevant in countries that offer a variety of seasonal activities such as Canada. The Minnesota Leisure-time Physical Activity (MLTPA) Questionnaire is the most commonly used of the quantitative history questionnaires, particularly for the study of lifetime physical activity due to its collection of information on months, frequency, and duration of activities from listed activity groupings (International Agency for Research on Cancer, 2002). Each activity is then multiplied by a MET value to determine a summary estimate. The majority of recent studies collect information about

recreational and/or occupational types of physical activity using comprehensive physical activity questionnaires that can take up to an hour to complete often with assistance from trained personnel. The amount of data that can take up to an hour to complete and often required assistance from trained personnel. The amount of data that can be collected by these self-reported questionnaires is limited by respondent fatigue and the reduced response rate associated with very long questionnaires.

Many terms have been used to characterize and estimate the intensity of physical activities in questionnaires, such as 'light, moderate, hard, or very hard'. Participants may be asked to estimate their perceived intensity or effort for each activity reported. Alternatively, the research may be limited to a specific intensity of activity, such as moderate and vigorous-intensity physical activity. These terms or estimates of perceived intensity are used as an estimation of energy expenditure (kJ/min), oxygen consumption (litres/min), or metabolic activity relative to resting activity (METs) (International Agency for Research on Cancer, 2002).

Failed memory and recall bias are potential problems when using questionnaire to estimate physical activity at earlier life stages. Because questionnaires have time frames ranging from one week (Sallis, 1985), to one year (Taylor, 1978) or even a lifetime (C. M. Friedenreich, Courneya, & Bryant, 1998), the respondent may have to spend considerable effort in recalling past physical activity details. In case-control studies, physical activity data are collected from cases following diagnosis while controls are selected with no such triggering event. This could increase the risk for differential recall bias (Spence et al., 2009). Cases may be influenced by their disease state in recalling and reporting past physical activity participation information. This would be most likely if they were sensitive to a lack of physical activity and believed that this may have contributed to their cancer. There has been no explicit study assessing the impact of

recall bias in case-control studies examining physical activity. The available information suggests that potential and magnitude of recall bias may depend on factors such as the type of physical activity performed, and the effect is likely minimal (Chouinard & Walter, 1995).

The type of physical activity may also influence the accuracy of recall. Recreational activities generally involve relatively short periods of higher intense activity. In contrast, occupational-related activities are typically sustained over much of an eight-hour work day. Occupational tasks are recalled with higher precision than recreational activities (International Agency for Research on Cancer, 2002). Other errors that can occur as a result of the questionnaire design include poorly worded questions, or phrasing of questions that could lead to misunderstanding or bias.

When physical activity questionnaires have been compared with detailed activity diaries, correlations have been approximately 0.5 to 0.6 (International Agency for Research on Cancer, 2002). This will lead to under-estimation of the true risk or benefit of physical activity on colorectal cancer risk (International Agency for Research on Cancer, 2002). The reliability of questionnaires tends to diminish with the length of the recall period (Shephard, 1990). This has been assessed by the test/retest correlations: two week coefficient of 0.86 for total physical activity (Lamb & Brodie, 1991); five-week coefficient of 0.88 (Folsam, Jacobs, Caspersen, Gomez-Marin, & Knudsen, 1986); 2-3 year coefficient of 0.59 (Slattery & Jacobs, 1995). Lack of reliability in longer recall periods may be due in part to seasonal variability and poor memory.

With regard to validity, physical activity questionnaires should ideally be valid in terms of its criterion validity. However, many studies rely on construct validity due to the absence of a universally accepted criterion. The most affordable construct is the use of a motion sensor such

as a pedometer or accelerometer. Regardless of the questionnaire selected, the data may have limited validity and reliability compared to laboratory or objective measures of physical activity.

3.2.2 *Movement monitors*

Pedometers aim to quantify ambulatory physical activity by accumulating steps (Ekoé et al., 2001). They are small battery devices typically worn at the waist and estimate movement at the trunk, though some are worn along the leg. They offer several advantages over other methods of physical activity assessment, including their relative precise estimates of activity, easy to use, small size, and low cost. There are several limitations in that they do not provide information about the type, duration or frequency of activities performed. Another limitation is their inability to detect arm movements, and their inability to be used in water. Thus, they would not be able to capture activities such as swimming, racquet-sports, or newer types of activity such as urban polling which use walking sticks to assist individuals keep upright during walking and increases the intensity (Colley et al., 2011). Their placement on the body affects their estimation of physical activity, and some models lack the sensitivity to detect movement in slower gaits (Ekoé et al., 2001).

Accelerometers are small, battery-powered devices worn on the waist, ankle, or arm. Unlike pedometers, they detect acceleration and deceleration in single or in multiple planes in addition to frequency of movement (Ekoé et al., 2001). Physical activity is expressed in terms of a ‘count’. They offer several advantages over pedometers in that they have the capability to record physical activity over a long time period and to document the patterns of activity (Ekoé et al., 2001). Like pedometers, there is no information obtained on type of activities performed.

Physical activity has been estimated in the Canadian Health Measures Survey using accelerometers. Participants wore the meters on their right hip on an elasticized belt during their waking hours for 7 days (Colley et al., 2011). It recorded time-stamped accelerations in all planes, thereby estimating intensity of physical activity in a count value per minute (Colley et al., 2011). Their accelerometers were also able to translate signals per minute into steps per minute. Published guidelines were followed to identify and remove days with invalid /incomplete wear time (Colley et al., 2011). Accelerometers have been validated in adult and children populations (Colley et al., 2011).

More recently, the use of the Fitbit accelerometers (Fitbit Inc., San Francisco, CA) has become a promising new technology for the measurement of physical activity. Their accuracy still needs to be evaluated for different physical activities in a non-laboratory setting. Based on laboratory walking or running, the hip-based Fitbit is very accurate at estimating step counts and is good at estimating energy expenditure (Diaz et al., 2015). The wrist-based Fitbit is less so for step counts (off by 10-15%) and energy expenditure (off by 35-50% depending on the exercise intensity) (Diaz et al., 2015).

Overall, objective measures of physical activity by devices such as pedometers or accelerometers tend to underestimate energy expenditure (Rubenstein et al., 2011), but tend to be significantly correlated with questionnaires (Ekoé et al., 2001). They cannot accurately capture activities that are largely different from walking or jogging (not step-based), such as biking or swimming.

3.2.3 Heart rate monitors

The use of heart rate monitors to estimate physical activity is based on the linear relationship between heart rate and oxygen consumption (VO_2) (Ekoé et al., 2001). Heart rate – VO_2 calibration curves are necessary for estimation of activity related energy expenditure because this relationship is attenuated during low and very high intensity activity (Ekoé et al., 2001). The calibration process is time consuming, but the use of the heart rate monitor following this is easy to use. Heart rate monitors are not as accurate as pedometers or accelerometers, and their use has been shown to influence physical activity behavior (Ekoé et al., 2001). Furthermore, several extraneous factors that influence heart rate also impact the accuracy of the heart rate monitors for the estimation of physical activity (e.g., medication, stress).

3.2.4 Other Methods

The measurement of physical activity using direct or indirect calorimetry is very accurate but are impractical for use in large epidemiological studies measuring physical activity due to associated costs and technical limitations (Rubenstein et al., 2011). Direct calorimetry is an accurate method in measuring energy expenditure (Kaiyala, 2014). It measures heat loss to assess body heat production, which will equal energy expenditure under steady-state conditions (Kaiyala & Schwartz, 2011). It is measured in a laboratory with the use of an airtight chamber over a 24 hour period followed by a 10-12 hour fasting (Ekoé, Zimmet, & Williams, 2001). Indirect calorimetry is the most common method employed to measure energy expenditure (Kaiyala & Schwartz, 2011). This method converts the measured rates of oxygen consumption (VO_2) and/or carbon dioxide production (VCO_2) into energy expenditure data (Kaiyala & Schwartz, 2011).

Double labelled water (DLW) technique is considered the gold standard in energy expenditure (Ekoé et al., 2001). It involves the digestion of isotopically labelled water, from which the amount of labelled water and oxygen can be measured over a set period of time (typically 1-2 weeks), and provides an estimate of carbon dioxide production (Ekoé et al., 2001). An estimate of physical activity is obtained by subtracting resting energy expenditure (obtained via indirect calorimetry in a laboratory). Once again, individuals must be confined to a metabolic chamber, but only for duration of assessment. It has the advantage of having no constraints on the setting of physical activity. However, this method of measuring physical activity is costly, and provides no information about the types of activities performed in the specified time period unless accompanied by an activity diary or questionnaire. Furthermore, repeated measures are required if used for more than 2 weeks (Ekoé et al., 2001). Overall, DLW is a non-practical use of long-term physical activity assessment.

3.3 Metabolic Equivalent Tasks (METs)

Physical activity is commonly quantified based on the metabolic equivalent (MET) value assigned based on laboratory study. A MET is defined as the ratio of the associated metabolic rate (measured from oxygen consumption) for a specific activity to the resting metabolic rate (International Agency for Research on Cancer, 2002). One MET for adults is the average resting energy cost and is set at 3.5 mL of oxygen consumed per kilogram of body weight per minute. An activity of 4 METs requires four times the amount of energy as compared to when the body is at rest. The Compendium of Physical Activities (Ainsworth et al., 2011) reports the MET value for a wide range of specific activities as multiples of one MET. The types of physical activities obtained from questionnaires may be used to identify and assign appropriate metabolic equivalents (METs) using these published values published.

The Compendium of Physical Activities is an accepted reference for quantifying energy costs associated with a variety of physical activities and for categorizing activities into sedentary, light, moderate, and vigorous intensities (i.e., 1.0-1.5, 1.5- 3, 3-5.9, ≥ 6 METs, respectively) (Csizmadi, Siou, Friedenreich, Owen, & Robson, 2011). Unfortunately, MET values are based on the energy expenditures of young adults and generally overestimate the metabolic costs of older individuals (Shepard, 2012). The compendium of physical activities lists activities in 21 categories, including the following categories which are particularly relevant for this study population: fishing and hunting, lawn and garden work, home activities, sports, and winter activities. Where available, the compendium highlights and references the MET values that are supported by published literature. As more research is conducted, the compendium updates its list with additional and current modes of physical activities.

Information on the length of time that an activity is performed and the frequency of performing it, can be combined with the MET value for the activity can be combined to estimate the total amount of energy expended on that activity. This will commonly be reported as MET-hours or minutes per week. Many studies incorporate this type of measurement, as it allows for greater variety of physical activity modes. Values can be combined across multiple activities to provide an estimate of total MET-hours/week from all types of recreational physical activity. Further details on the calculation of MET-hours/week are provided in Chapter 3 (Methods).

4. Lifetime Physical Activity and CRC Risk: Review of the Literature

Over 60 studies have provided convincing evidence that physical activity reduces the risk of CRC (C. M. Friedenreich et al., 2010). The majority of the literature has focused on physical

activity measures in the time period within 2 years of the disease diagnosis, a time period that may not be relevant for a disease with a long latency period such as CRC. The influence on CRC risk of age when a subject engaged in physical activity is unknown. The literature to date has generally failed to examine fluctuations or changes in physical activity participation over time. Compelling evidence is unfolding that the timing of exposure to several factors, including folate, smoking, and calcium, may influence CRC risk differentially (Wei, Wolin, & Colditz, 2011). The potential for a similar effect with physical activity requires exploration.

The current literature review will focus on the few existing studies that measured lifetime recreational physical activity and CRC risk. There are two benefits of investigating lifetime physical activity and CRC risk:

1. There is opportunity to study the correlation between physical activity in different time periods, which can help our understanding in lifestyle behavior and drive appropriate interventions
2. Analyses may be performed to investigate the effect of consistently high (or low) physical activity throughout the lifetime on risk, compared with those who may be highly active in only one or two life periods

The literature search identified 9 studies (five case-control studies and four cohort studies), which have examined lifetime recreational physical activity and the risk of CRC. One systematic review based on cohort studies that assessed lifetime total physical activity and CRC was also included in the current review (Robsahm et al., 2013). The search was limited to Pubmed, using the terms “colon, rectal, or colorectal cancer, and physical activity, exercise or recreation up until December 2013. All studies were limited to those that included the word ‘lifetime, lifespan, or age period(s)’ in the abstract, or it was suggested that lifetime activity was

assessed from the abstract, but the search was not systematic in nature. The focus of this literature review is on case-control studies since it will provide a reference for future discussion comparing our results to other case-control studies that investigated the association between lifetime recreational physical activity and CRC risk. The characteristics of the 9 studies that examined lifetime recreational physical activity are presented in Tables 2 and 3.

4.1. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies (Robsahm et al., 2013)

Only one systematic literature review included an analysis of ‘lifetime’ physical activity and CRC risk (Robsahm et al., 2013). The systematic review and meta-analysis was limited to cohort studies that provided risk estimates and corresponding confidence intervals for the risk of the proximal and distal colon separately. The cohort studies ranged from 5-15 follow-up years, with each of the populations having a baseline mean age in their mid-forties or fifties.

Four cohort studies within this review reported risk estimates with respect to lifetime total physical activity (C. Friedenreich et al., 2006; Larsson, Rutegard, Bergkvist, & Wolk, 2006; Severson, Nomura, Grove, & Stemmermann, 1989; Thune & Lund, 1996). None of these studies assessed the variation or patterns of activity performed across the lifetime, nor did they assess physical activity separately for different time periods (e.g., early, mid, and late adulthood). Thus, these studies computed lifetime cumulative activity scores. Two of these studies only included males (Larsson et al., 2006; Severson et al., 1989).

The meta-analysis based on these 4 studies found a significant inverse association between ‘lifetime’ total physical activity (recreational and occupational) and each of the colorectal sub-sites. The strongest effect was observed for proximal colon cancer (RR=0.32, 95% CI: 0.24-0.43), with a lower effect for distal colon cancer (RR= 0.48, 95% CI: 0.37–0.62).

Table 2. Review of selected cohort studies assessing lifetime recreational physical activity and CRC risk

First author, year	No. cases	Average follow-up years	Exposure category	Adjust by occupational PA (Y/N)	Disease end-points ^a ; RR (95% CI)
Friedenreich et al., 2006	1.094 CC; 599 RC	6.4	<12 vs. >42.8 MET-hours/wk)	Y	CC : 0.88 (0.74-1.05) RC: 1.02 (0.73-1.44)
Larsson et al., 2006	496 CRC	7.1	< 10 vs. ≥60 minutes/ day (average)	Y	CC : 0.56 (0.37–0.83); RC : 0.59 (0.34–1.02)
Thune & Lund, 1996	335 CC; 228 RC;	15	regularly active vs. inactive	N	CC: 1.33 (0.90-1.98) RC: 0.98 (0.60-1.61)
Severson et al., 1989	192 CC; 95 RC	2	Highest vs. lowest tertile	N	CC: 0.71 (0.51-0.99) RC: 1.41 (0.84-2.36)

^a DCC=distal colon cancer, PCC= proximal colon cancer, CC = colon cancer, RC=rectal cancer

The results also found a significant risk reduction for rectal cancer among individuals in the highest physical activity quartile across the lifetime (RR=0.69, 95% CI: 0.57-0.84). They did not assess this association separately for recreational and occupational physical activity. The I^2 for rectal cancer and lifetime physical activity studies was 0%, suggesting there is unlikely any variability in effect estimates that is due to heterogeneity rather than sampling error. This contrasts with distal and proximal colon cancer studies that result with an I^2 of 31.0 and 22.5, respectively. The authors concluded that lifetime total physical activity is associated with a significant inverse colon cancer risk, and possibly associated with an inverse risk of rectal cancer.

All cohort studies included in their systematic review combined recreational and occupational physical activities (total physical activity) to assess cumulative ‘lifetime’ physical

activity and CRC risk. Some of the studies (Table 2) assessed recreational physical activity and CRC separately. Following our search, no cohort study to date has assessed the association of recreational physical activity and CRC using more than 15 years of data collection.

4.2. Case-control studies examining lifetime physical activity and CRC risk

4.2.1. Occupational and recreational physical activity during adult life and the risk of cancer among men, (Parent et al., 2010)

This population-based case-control study assessed the risk of cancer at 12 different sites among men aged 35-70 years (Parent et al., 2010). There were 495 incident colon cancer cases and 248 rectal cancer cases recruited from 18 Québec hospitals. A total of 533 controls from the general population were recruited using electoral lists and were randomly selected. Interviews were conducted mostly face to face, in a two part series less than 12 months following diagnosis for cases and over same period for controls. Physical activity was measured using questionnaires to collect recreational and occupational physical activity histories. The study obtained considerable detail for occupational physical activity. However, their assessment of recreational physical activity during adult life was collected without eliciting much detail. Participants were asked, “During your adult life, did you spend any of your spare time on sports and/or outdoor activities?” Response choices were: ‘never or not often’, or ‘often’. ‘Often’ was defined as, ‘an average of once a week or more for at least 6 months’. The latter represented a crude estimate of ‘often’ engaging in recreational activities in their adult lifetime. No details about the specific recreational activities were collected.

Physical activity was recorded for lifetime recreational and lifetime occupational activity. Analyses were conducted separately for both types of activity. The authors stated there were no substantial differences in risk estimates when type of physical activity was included in the fully-

adjusted models (data was not shown). The odds ratios for lifetime recreational physical activity when comparing ‘often’ with ‘never active or not often’ was 1.07 (95% CI: 0.81-1.41) for colon and 0.91 (95% CI: 0.56-1.27) for rectum. The issue of misclassification among those who don’t fall under an ‘extreme’ category is possible, as individuals were required to choose between ‘never or not often’ or ‘often’. This was the only study that failed to demonstrate a significant inverse association between lifetime recreational physical activity and colon cancer. High levels of lifetime occupational physical activity (>75% work years spent in very active jobs) was significantly associated with colon cancer (OR: 0.58, 95% CI: 0.34-0.99), but not rectal cancer (OR=0.66, 95% CI: 0.34-1.29).

4.2.2. Timing and intensity of recreational physical activity and the subsite-specific colorectal cancer (Boyle et al., 2011)

Boyle et al. (Boyle et al., 2011) estimated the effects of recreational physical activity performed across the adult lifetime on the risk of distal and proximal colon cancer, and rectal cancer. This was part of the Western Australian Bowel Health Study which consisted of 870 cases and 996 controls. Cases were ascertained from a cancer registry, while age- and sex-matched controls were randomly selected from an electoral roll for the same time period. Physical activity data was collected through a self-administered comprehensive physical activity questionnaire. Participants were asked to record recreational physical activities that they performed more than 10 times during each of listed periods in their lives. Information about activity levels and ‘dose’ was also collected, including number of years, months per year, and hours per week. The authors derived a total MET-hours per week for each time period. The study examined risk associated with PA within three different age ranges: 19-34 years, 35-50 years, and 51 years and older.

The study found that people who consistently performed 6 or more MET-hours per week of vigorous physical activity across the adult lifetime had a statistically significant reduced risk of distal colon cancer in both men and women when compared to those who regularly did none or little vigorous activity across the lifetime (OR=0.59, 95% CI: 0.36-0.96). The risk of proximal colon cancer was not associated with physical activity in any specific time period (e.g., early, middle, or later adulthood), or with consistent physical activity across the lifetime (OR=0.93, 95% CI: 0.59-1.45). The study also found protective results for rectal cancer in men, (OR=0.50, 95% CI: 0.28-0.89), but not for women (OR=1.04, 95% CI: 0.47-2.30). The study also examined continuity of participation in vigorous activity. The significant association among men did not exist if vigorous activity was performed only in one age period. They found the strongest protective effect was associated with vigorous-intensity physical activity in early adulthood (19-34 years) among women (distal colon cancer OR=0.49, 95% CI: 1.21-1.17) and in mid-adulthood (35-50 years) among men (distal colon cancer OR=0.55, 95% CI: 0.30-1.00).

The authors also compared vigorous and moderate intensity activities. The results suggest moderate intensity activity alone was not associated with reduced risk for proximal or distal colon cancer, or rectal cancer, for any time period. Furthermore, consistently high levels of moderate activities throughout the adult lifetime were not associated with a reduced risk of proximal colon cancer, distal colon cancer, or rectal cancer. This may be an important public health message suggesting activities such as walking, which is one of the most common modes of physical activities (World Cancer Research Fund/American Institute for Cancer Research, 2011), is not sufficient to decrease CRC risk.

4.2.3. Case-control study of lifetime occupational and recreational physical activity and risks of colon and rectal cancer (Steindorf et al., 2005)

Steindorf et al., 2005 (Steindorf et al., 2005) was conducted in Poland and aimed to assess total physical activity (i.e., recreational and occupational physical activity) at different age periods and across the adult lifetime, as well as at different periods preceding cancer diagnosis for colon and rectal cancer risks separately. This study assessed recreational and occupational physical activity and undertook separate sub-group analyses. The study included 239 incident CRC cases (98 colon and 141 rectal cancers) and 193 controls (cancer-free patients) who were randomly selected from a Polish hospital.

Physical activity was measured via standardized questionnaires during an interview. Participants were asked to recall recreational (and occupational) physical activity starting at age 20 through to their 60s. Specifically, participants were asked to report the average time spent for a prepared list of recreational activities: walking or hiking, biking, gardening, practicing sports, or household activities. These were assessed separately for summer and winter seasons and then averaged in their analysis. Occupational activity was collected using cruder categories: no or light activity, moderate, or heavy work performed on most days of the week. MET-hours per week were used to classify each participant into quartiles based on controls.

When recreational physical activity was assessed separately from occupational physical activity, there was no significant association between physical activity and colon cancer (OR: 0.82, 95% CI: 0.36-1.90) when comparing the highest lifetime recreational activity quartile (>74.4 MET-hours per week) to those in the lowest quartile (<23.2 MET-hours per week). Comparably, there was a significant inverse association between highest lifetime occupational

activity quartile (>146.7 MET-hours per week) and colon cancer compared to the lowest quartile (0 MET-hours/week).

This was the only study that assessed the effect of total energy intake on the association between lifetime (total) physical activity and colon and rectal cancer, by collecting lifetime lifestyle and dietary factors. They found the risk reduction for colon cancer in group with the highest tertile of physical activity was more pronounced among the highest energy intake group (OR=0.39, 95% CI: 0.16-0.95), compared to the lowest energy group (OR=0.63, 95% CI: 0.22-1.83). This finding is in agreement with other studies (Levi, Pasche, & Lucchini, 1999; Slattery et al., 1997). No other factors were considered effect modifiers.

In addition to lifetime physical activity, significant reductions in risk was also observed for people whose activity was classified in the highest physical activity quartile at age 30, 40, and 50, and for 10, 30, and 40 years prior to diagnosis of colon cancer. The greatest risk reduction for any one time period was found for those who were in the highest physical activity quartile during their 50s. This study did not find a consistent association or significant trend between physical activity and rectal cancer at any age or time period including lifetime measures.

4.2.4. Physical activity and colon cancer: a public health perspective (Slattery et al., 1997)

Slattery and colleagues (Slattery et al., 1997) examined the association between physical activity and colon cancer. The study predominantly looked at ‘long-term’ physical activity but also included an analysis that considers lifetime physical activity. Cases were identified from the Kaiser Permanente Medical Program of Northern California, Utah, and Minnesota. Controls

were matched by sex and 5-year age groups and came from same population. Neither sample size nor specific numbers of cases and controls were reported.

Table 3. Review of case-control studies assessing lifetime recreational physical activity and CRC risk

	Age-periods	Exposure category	Disease end-points ^a	Occupational PA adjusted (Y/N)	Analysis by sex (Y/N)	Patterns of lifetime PA evaluated (Y/N)
Boyle et al., 2011	19-34; 35-50; 51+	MET-hours/wk	DCC, PCC, RC	Y	Y	Y
Parent et al., 2011	'adult lifetime' (not specified)	Never/not often vs. often	CC, RC	N	N/A	N
Marcus et al., 1994	14-18; 18-22	None vs. any	CC, LCC, RCC	N	N/A	N
Slattery et al., 1997	2, 10, 20 yrs < ref. date	Ranking: calories expended/wk	CC	N	Y	N
Steindorf et al., 2005	20-50s (by decade); 20-50 yrs < ref. date)	MET-hours/wk	CC, RC	N	N	Y

^aDCC=distal colon cancer, PCC= proximal colon cancer, CC= colon cancer, RC = rectal cancer, LCC=left, RCC =right

They collected physical activity for four different ages (i.e., referent year, 2 years prior to referent date, 10 years ago and 20 years ago) to develop a 'long-term' physical activity, and 'lifetime' vigorous recreational physical activity score. Participants were asked to recall activity patterns at home, work, and at leisure using an adapted version of the CARDIA physical activity questionnaire (Slattery & Jacobs, 1995). Participants were asked if they performed moderate and vigorous activities for at least 1 hour total time in any month of the referent year. Moderate

activities were loosely defined as, “activities done at a more moderate pace than more strenuous activities”, whereas strenuous activities were considered, “activities that make you sweat or get out of breath”. The interviewers provided 4 categories of moderate activities and 8 categories of vigorous activities with examples, and provided examples of light activities that were asked not to include.

For each activity provided, dose parameters were collected including months per year, hours/minutes per session, and average number of days per week. The authors created a summary variable that ranked people on their overall amount of long-term activity by converting frequency and average time into energy expenditure. For example, non-active individuals were ranked ‘1’, while those expending >1,000 calories/week were ranked the highest score of ‘4’. Each participant was given a rank for each time period or age, and then were added together to obtain a summary estimate. Summary rankings of ‘1’ were considered sedentary for the last 20 years whereas the highest rankings were considered to have the highest levels of physical activity in the past 20 years.

When compared to participants who were sedentary throughout the lifetime, high levels of vigorous recreational physical activity were associated with a significant ~40% risk reduction for all participants (OR: 0.62, 95% CI: 0.52-0.75). The inverse association was greater among individuals without a positive family history of CRC compared to individuals with a positive family history of CRC. This study is consistent with the literature which suggests the greatest protection against colon cancer comes from involvement in physical activities that are of a more intense nature than moderate intensity (C. M. Friedenreich et al., 2010; Wolin et al., 2009).

5. Discussion

The literature review focused on studies that investigated lifetime recreational physical activity and CRC. The focus was on recreational physical activity in order to better compare and contrast methods and findings with the current study. Furthermore, the methods used to measure occupational physical activity currently present with significant challenges and limitations.

All of the existing case-control studies that have investigated physical activity across the lifetime have found protective effects of lifetime recreational or total vigorous physical activity against colon cancer or one of its subsites. The risk reduction for colon cancer ranges from 32% to 74%. The variation observed may reflect differences in how lifetime physical activity is measured and type of population studied.

Most studies collected physical activity using adapted physical activity questionnaires that have been previously shown to be reliable and/or valid. Likewise, most authors use MET-hours per week to quantify physical activity. These estimates are then categorized into quartiles or quintiles based on the activity levels of the control group. The main difference between the studies is whether they used an average MET-hours/week as an estimate of lifetime physical activity, or whether they use consistent patterns of physical activities performed across the lifetime. Two studies assessed both average MET-hours/week across the lifetime, and consistent patterns of activity across the lifetime (Boyle et al., 2011; Steindorf et al., 2005). The overall evidence suggests consistently participating in vigorous physical activity for each age period provides greater protection against colon cancer than engaging in vigorous physical activity in only one or two life periods (Steindorf et al., 2005). Furthermore, the studies suggest vigorous

intensity physical activity results in greater colon cancer risk reductions compared to moderate intensity activities.

Four of the 5 case-control studies investigated rectal cancer as a separate disease endpoint. Most studies found no association between physical activity and rectal cancer at any age or time period including lifetime vigorous recreational physical activity measures. One study found a protective effect on rectal cancer: high levels of vigorous recreational physical activity (≥ 18 MET-hours/week) between the age period 35-50 years significantly reduced the risk of rectal cancer by 37%, compared with those doing no vigorous activity (Boyle et al., 2011). Furthermore, Boyle et al found a significant 50% risk reduction in rectal cancer among men who reported physical activity participation which was always within the highest quartile of vigorous PA across the adult lifetime. No association between lifetime vigorous activity and rectal cancer was found among women. These observed differences in risk estimates may be due to the fact that the study by Boyle et al., 2011 adjusted for lifetime occupational physical activity along with other covariates to assess the association between lifetime recreational physical activity and rectal cancer risk. The population source may also partially explain the differences in results or amplitude of the overall effect across the studies. Only two studies considered the effect of family history on CRC risk. Finally, there is some evidence to indicate the risk reduction is greatest among those with high caloric intake and no family history of CRC (Slattery et al., 1997).

Thus, the existing research available on lifetime physical activity and CRC has several limitations. The definition for what constitutes consistent, or 'regular', physical activity varies from study to study. Studies that investigate lifetime physical activity tend to use more crude definitions, such as 'more than 10 times during each time period', or 'performing moderate or

vigorous intensity activity for at least 1 hour total time in any month of reference year’, ‘an average of once a week or more for at least 6 months during each time period’, or ‘that requires stamina and strength’. Only one study considered variation in physical activity levels across the lifetime (Boyle et al., 2011), whereas a second study only looked at consistent patterns of physical activity throughout the lifetime (Steindorf et al., 2005) which excludes any participant whose activity levels changed over time. None of the cohort studies included in the recent systematic review examined the potential risk of CRC associated with participation in physical activity at different age or time periods, but this may be due to restrictions of data collection to follow-up years. Another limitation of the existing studies is the lack of clarity in reporting on whether or not they use open and/or closed-ended questions in their questionnaires. Only 1 study (Boyle et al., 2011) appeared to have included open-ended questions. An open-ended format provides the advantage of capturing seasonal, cultural, and individual diversity in activities. Furthermore, the inclusion of an open-ended format allows for greater exploration into the mechanism of how physical activity protects against CRC, by examining the type of activities performed by the study population.

One consideration when assessing lifetime physical activity is deciding whether or not to combine occupational and recreational physical activity. For example, one study that assessed total physical activity (recreational and occupational physical activity) summed the MET-hours per week score using detailed recreational activity data and crude measurements of occupational physical activity (Steindorf et al., 2005). Due to the challenges that exist with measuring occupational physical activity, many studies have assessed recreational and occupational types of activities separately.

5.1. Gaps in the literature

Relevant aspects of the universally recognized and accepted inverse relationship between physical activity and CRC are still unclear. Based on the studies examined in this review, it is likely that sustained participation in vigorous physical activity throughout a person's lifetime results in greater risk reductions for colon cancer than does intermittent physical activity throughout the lifetime. There is conflicting evidence of whether this association also exists for rectal cancer. There is also uncertainty regarding how the physical activity and CRC relationship is affected by other factors including sex, and familial history of CRC. Only two studies investigated different patterns of physical activity across the lifetime, and no study has explored the effect of not participating in moderate or vigorous physical activity consistently throughout the lifetime on CRC risk. This thesis will investigate lifetime physical activity and CRC risk and will consider factors such as sex, cancer sub-type, as well as different patterns of physical activity performed across the lifetime.

CHAPTER 3: POPULATION-BASED CASE-CONTROL STUDY METHODS

1. Study Design

The current study is a secondary analysis of data on recreational physical activity across the lifetime and colorectal cancer (CRC) risk in Newfoundland and Labrador, Canada.

2. Data source: The Newfoundland Colorectal Cancer Study

This study used data collected from an existing population based case-control study from Newfoundland and Labrador. The data were collected as part of the large population-based Newfoundland and Ontario Colorectal cancer study (NOCS), which examined the risk of CRC in relation to personal health and diet/lifestyle factors collected using self-administered questionnaires.

Cases for the Newfoundland and Labrador study were recruited using the Newfoundland and Labrador provincial cancer registry. The case group formed the Newfoundland and Labrador Colorectal Cancer Registry (NFCCR). The NFCCR is modeled after the NIH-supported Colorectal Cancer Registries and specifically, the Ontario Familial Colorectal Cancer Registry (OFCCR) (Green et al., 2007; Woods et al., 2010).

The NFCCR was established in 1999 to investigate factors suspected to be responsible for the historically high age-standardized CRC incidence rates among men and women in Newfoundland and Labrador (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015; Green et al., 2007). Newfoundland and Labrador have the highest incidence rate of CRC in Canada. They also have among the highest rate of familial CRC in the world (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015; Woods et al., 2010).

The methods used to complete the population-based case-control study assessing the association between physical activity across the lifetime and the risk of CRC are as follows:

2.1. Case and control ascertainment

2.1.1. Cases

The NFCCR identified all incident cases of CRC through their provincial cancer registry which is maintained by the Newfoundland Cancer Treatment and Research Foundation. Eligible cases included every Newfoundland and Labrador resident diagnosed with histologically confirmed primary adenocarcinoma of the colon or rectum (International Classification of Diseases 9th rubric: 150.0-153.9, 154.1-154.3, and 154.8; or 10th rubric: C18x, C19, and C20) diagnosed between January 1, 1999 and December 31, 2003. Exclusion criteria included carcinoid tumors, carcinoma in situ, recurrent cancers, and individuals diagnosed at 75 years of age or older (Green et al., 2007). The study collected 695 case subjects who completed at least some of the study questionnaires.

2.1.2. Controls

Control participants were Newfoundland and Labrador residents who were identified through random digit dialing (RDD) between 1999 and 2003. Control selection was frequency matched to cases on sex and 5-year age strata. The study recruited 706 controls.

2.2. Data Collection

Once verbal consent for participation was obtained (primarily through telephone contact), questionnaires were mailed to eligible participants with self-addressed stamped envelopes (Zhao et al., 2010). Eligible participants were invited to participate in the NRCCR study by completing three self-administered questionnaires: a personal history questionnaire (PHQ), a food frequency questionnaire (FFQ), and a family history questionnaire (FHQ). They were also provided with

information regarding the study and a consent form. For cases who had died prior to the interview, the study coordinator sought the participation of a close relative (a proxy) for the purpose of obtaining family history and for permission to access medical records (Woods et al., 2010). If a participant had not returned finished questionnaires within 3 weeks or there were responses that needed clarification, follow-up telephone calls were made to participants (Zhao et al., 2010). A telephone interview or other assistance was offered when illiteracy or other barriers were an issue.

The PHQ consisted of 74 questions that collected data on medical, demographic, lifestyle, pharmacologic, menstrual and reproductive, and anthropometric factors (Appendix 1). The FHQ was used to collect information from the participants on the type of cancer diagnosis (ICD9 codes), and family history of CRC. The FHQ was also sent to participant's family members who had a personal history of cancer, to collect additional familial medical information. Finally, the FFQ was developed from the FFQ used among the Ontario study that used the same methods, but was adapted to include food items unique to the province of Newfoundland and Labrador (Squires et al., 2010). The FFQ was not used for our analyses.

3. Current Study Methods

3.1. Inclusion/Exclusion Criteria

A total of 1401 eligible participants (695 cases, 706 controls) consented to the study and completed at least a portion of the Personal Health Questionnaire (PHQ) in the original NFCCR study. The current study excluded 6 participants (3 cases and 3 controls) who were less than 30 years of age, The final study samples consists of 1395 people (692 cases and 703 controls).

Some cases were missing the ICD9 code to designate their detailed cancer subsite (n=39). They were retained for the primary analyses (which ignored subsite) but excluded in the analysis that was restricted to colon cancer.

3.2. Study Outcomes

The primary outcome of interest is colorectal cancer (CRC). A secondary analysis was made for colon cancer specifically.

3.3. Physical Activity Data Collection

The main exposure of interest is moderate and vigorous recreational, or leisure-time, physical activity. This was measured by self-reported data from the PHQ. Participants were asked to recall their recreational physical activities during three age periods: their 20s, 30-40s and where applicable, since they turned 50 (Appendix 1). They were asked to recall their activity levels for a list of 9 different moderate or vigorous recreational or household physical activities: walking, jogging, running, biking, swimming laps, tennis/squash/racquetball, calisthenics/aerobics/vigorous dance/rowing machine/weight lifting, football/soccer, rugby/basketball, and heavy household work. For each activity category, participants were asked the following set of questions:

“In your 20,s, 30-40’s, and since turning 50, did you participate regularly in physical activity for a total of 30 minutes a week?”

If yes, for how many years and months per year, and during those months on average, for how many minutes (or hours) per week?”

Of these 9 activities, heavy household work was excluded from all analyses since it was not considered recreational in nature and contained data errors such as implausible hours or levels of

activity per week, along with higher rates of missing values compared to the other physical activities.

Subjects were also asked to provide information about other strenuous activities in which they engaged regularly but which were not included in the list provide to them. This second set of physical activity questions was open-ended, which provided an opportunity for participants to list additional types of “strenuous activities” in which they participated. They were asked:

“In your 20,s, 30-40’s, and since turning 50, did you do any other strenuous activities? (Strenuous activity means something that really increased your heart rate, made you hot, and caused you to sweat. Some examples are: skiing, skating, hunting, sledding or tobogganing, water-skiing)”.

Information about occupation was collected in the PHQ. However, there was insufficient information to quantify occupational physical activity. This factor will not be considered further.

3.4. Derivation of Physical Activity Estimates

The raw data on physical activities undertaken by each subjects was converted into summary measures of activity that take into account the intensity of the activity and the frequency with which it was undertaken. One measure was created for each age period (20-29, 30-49 and over age 50).

The reported physical activity was converted into a standard activity measure with units of MET-hours/week. An estimate of activity was created for each age interval. A lifetime average activity was also created. This is an estimate of the average number of MET-hours expended per week over the specific age interval. It combined information from all activities into a summary measure. Thus, for example, consider a person whose only activity for the age

interval 20-29 was reported as walking for 2 hours per week, every week of the year for every year during their twenties. Walking has a MET value of 3.5. The activity measure for this person would be calculated as: 7 MET-hours per week = 3.5 METs * (2 hours/week) * (12 months/year * 100% of the age period from 20-29).

The process of creating these measures is described in the next sections.

3.4.1. *Assignment of MET value to activity estimates*

The first step in creating the activity score was to assign appropriate metabolic equivalents (METs) using values published in the Compendium of Physical Activities (Ainsworth et al., 2011) for each type of recreational physical activities obtained from the PHQ. In accordance with methods used previously by Giovannucci et al., (Giovannucci et al., 1995) an average MET value was assigned to categories that listed more than one type of activity in the questionnaire (e.g. tennis, squash, or racquetball). For any activity listed in the compendium, the general form of the activity was used to assign a MET value, unless details were provided to suggest otherwise. For example, the open-ended questions often provided some details in the response, such as “rowing in the regatta”. This type of response refers to training and a subsequent competition for which the MET value assigned is typically higher than the general form of rowing. The general form of an activity is typically a more conservative estimate and offers the advantage of consistency for exposure measurement. Hence, the overall level of activity may be under-estimated. If more than one ‘general’ form is presented with evidence from published literature, then the mean MET value is assigned. If two different intensities were listed in the compendium, (e.g. snow shoeing (moderate effort vs. vigorous effort)), the more conservative estimate was selected.

3.4.2. *Calculating MET-hours/week for each activity in each age period*

In order to estimate the MET-hours/week for an activity, the assigned MET value has to be multiplied by the time that the subject engaged in the activity. This time is the number of hours per week engaged in the activity, averaged over the entire interval. This was operationalized from the reported number of hours spent on an activity, adjusted for an ‘activity fraction in the interval’. The ‘activity fraction in interval’ was determined by multiplying the proportion of the year reported as active (i.e. months per year/12) by the proportion of the number of years spent active within the timeframe specified (i.e. reported active years/eligible active years in timeframe). Since all participants in this study are 30 years or older, the eligible active years during their twenties was 10 years. The eligible active years during their thirties and forties were determined by calculating the difference between 30 and their age for individuals less than 50 years; it was 20 for people 50 years or older. For the age interval of 50 years or older, the eligible active years were determined by calculating the difference between 50 and their age. For individuals who were age 30 years or 50, 0.5 years was assigned as their eligible active years.

The amount of time (in hours) spent doing each activity in a week was used to multiply the MET value for the activity to generate a MET-hour/week estimate for each activity. The average MET-hours per week were then calculated by multiplying the MET-hours of each activity by the ‘activity fraction in interval’ within the eligible timeframe.

3.4.3. *Calculating total physical activity in an age period*

The total physical activity measure was computed by combining the activity-specific estimates. The activity specific average MET-hours per week were summed to provide the total

average MET-hours per week for each age period. This process can be summarized in the following formula:

$$\text{Average MET/week} = \sum \text{METs} \times \frac{\text{hours}}{12} \times \frac{\text{days}}{\text{years}}$$

3.4.4. *Inclusion of open-ended activities*

Participants had the opportunity to list other strenuous physical activities in an open-ended format. Participants were able to list up to 6 other strenuous activities in addition to the 8 close-ended physical activities, for a maximum of 14 physical activities. An activity reported in this question was excluded from analysis if the assigned MET value was less than 3 METs, if the activity listed was too ambiguous to assign it a MET value (e.g., work), or if it was clearly defining an occupation or work-related task (e.g., surveying).

3.4.5. *Lifetime physical activity estimation*

The average lifetime MET-hours per week was determined by combining the estimated physical activity within each age interval. Since the intervals were of different lengths, a weighted averaging process was used. Each interval was weighted by the eligible active years in the interval (see above). These weighted values were summed and then dividing the score by the total number of years spent in their adult lifetime. The number of years in the adult lifetime was determined by the difference between 20 and the age at which they completed the PHQ.

This can be summarized in the following formula:

If age < 50:

Average lifetime MET-hours/week=

$$\frac{(20s \text{ MET score} * 10) + (30 - 40s \text{ MET score} * \text{eligible active years})}{(\text{age} - 20)}$$

If age ≥ 50:

Average lifetime MET-hours/week=

$$\frac{(20s \text{ MET score} * 10) + (30 - 40s \text{ MET score} * 20) + (50s \text{ MET score} * \text{eligible active years})}{(\text{age} - 20)}$$

3.4.6. *Categorization of Physical Activity*

Estimated physical activity (MET-hours/week) for each age period (20s, 30-40s, 50s) and over the lifetime was categorized into quartiles, based on the distributions of cases, in accordance with the approach to maximize statistical power to detect an anticipated inverse association proposed by Heish et al. (1991). Participants who reported no activity (MET-hr/week = 0) were assigned to a separate category. Thus, there were five groups, with quartiles defined among active participants, leaving 'no activity' as a reference group.

3.4.7. *Patterns of physical activity across the lifetime*

We analyzed different lifetime patterns of physical activity. In order to investigate the effect of different lifetime patterns of recreational physical activities, a new variable was created with five levels:

- i. Participants who were consistently non-active (0 MET-hours per week) for every age period were classified as “always no activity”. It is important to note these individuals may have engaged in light activities (<3 METs), but were classified as ‘no activity’ since our analyses are restricted to moderate and vigorous activity only;
- ii. Participants who had some activity but were always classified in one of the three lower activity categories for every age period were classified as “always low or no activity in 1-2 age periods”;
- iii. Participants who were in one of the higher two categories in only one age period were classified as “high activity in one age period”;
- iv. Participants who were in one of the higher two categories for two of the three age periods were classified as ‘high activity in two age periods’;
- v. Finally, participants who were in one of the two higher activity categories for each age-period were classified as “always high activity”.

This categorization been used previously by Boyle et al., 2011, with minor differences with regard to their reference group (they used a ‘no or always low physical activity’ as reference, compared to our ‘always 0 MET-hours/week’ reference category).

3.5. Covariates

Potential confounders for this study were determined a priori and were based on convincing or probable evidence that they protect against or increase the risk of CRC. Evidence for risk factors were obtained from the WCRF/AICR Second Expert Report and Continuous Update Project (CUP)(World Cancer Research Fund / American Institute for Cancer Research 2007), reports from International Agency for Cancer on Research, and accumulating evidence for diabetes from systematic reviews (Larsson et al., 2005; Sun & Yu, 2012).

Covariates used in the main analyses are: age (continuous), sex (male, female), procedures to detect colorectal cancer (i.e., sigmoidoscopy, colonoscopy, or FOBT) (yes/no), inflammatory bowel disease (IBD: Crohn's disease or ulcerative colitis) (yes/no), active tobacco smoking (never/current/former), type 2 diabetes (yes/no), regular aspirin use (yes/no), regular folate use (yes/no), regular calcium use (yes/no), BMI (underweight and normal/overweight/obese), and alcohol consumption (ever/never for each age period or for lifetime when lifetime analysis was performed). Each of the variables included in the models is listed below, with a description of how it was measured and coded in the final models.

3.5.1. *Age and sex*

Both age and sex were self-reported. Age was entered in the models as a continuous variable.

3.5.2. *Body Mass Index (BMI)*

Self-reported Body Mass Index (BMI) was used as a measure for abdominal fat or total body fat. BMI was derived from respondents' self-reported height and weight, and was calculated as follows: $BMI = [\text{body weight (kilograms)} / \text{height (meters)}^2]$. Two BMI indices were used for analyses. The first was recent BMI, which was calculated from body weight during the reference period (2 years prior to diagnosis for cases and 2 years prior to participation for controls). The second was BMI at age 20, which was calculated from their self-reported body weight at 20 years. BMI at age 20 was used for the analyses during the 20s; all other time periods used the recent BMI measures. BMI was categorized as follows: ≤ 24.99 , 25-29.99, ≥ 30.0 , which reflects normal/underweight, overweight, and obese, respectively.

3.5.3. *Drinking alcohol*

Heavy alcohol consumption is considered a risk factor for CRC (IARC, 2012). Alcohol consumption was measured for each decade throughout the adult lifetime. Within the PHQ, data were collected on beer, wine, sake and spirit/liquor consumption for each timeframe. For each type of alcohol. Participants were asked if they had ever drunk it (ever/never) and, if so, the estimated amount they drank. We derived a variable to indicate if the person ever drank at least one alcoholic drink per week for six months (ever/never) for each age period. This was aggregated for lifetime drinking. Alternate drinking variables were considered to quantify alcohol (i.e., beer, wine, sake, and spirit/liquor) consumed per unit of time. However, there were considerable missing data (>25%) which rendered these options unsuitable for use.

3.5.4. *Smoking*

Smoking was categorized as never, current, and former in the fully-adjusted models. Participants were asked, ‘have you ever smoked at least one cigarette for 3 months or longer?’ Those who did not smoke were classified as never smokers. Current smokers were defined as having smoked at least one cigarette a day 2 years prior to questionnaire. Former smokers were based on participants who reported they stopped smoking permanently as of two years ago.

3.5.5. *Calcium, aspirin, and folic acid/folate supplementation*

Participants were asked if a doctor had ever told them they had diabetes or diabetes mellitus. Respondents were categorized as ever/never for inclusion in the full-adjusted models. Likewise, the same question was asked for aspirin (such as Anacin, Bufferin, Bayer, Exedrine, Ecotrin) and folic acid or folate pills/tablets.

3.5.6. *Diabetes and inflammatory bowel disease (IBD)*

Participants were asked if a doctor has ever told them they had diabetes (also known as diabetes mellitus). It was noted this did not include diabetes that occurred only during pregnancy. Respondents were classified as ever/never. Likewise, they were asked if a doctor ever told them that they had Crohn's disease. A separate question was asked about ulcerative colitis. If a participant reported yes to either of these latter two conditions, the participant was reported as ever having IBD. IBD was classified as ever/never.

3.6. Data Processing

Several databases from the NFCCR study were provided. The data included were from the three separate questionnaires. Due to the large volume of open-ended questions related to physical activity in addition to mixed type data (e.g., both numerical and categorical), a significant amount of data transformation and cleaning steps were executed. In order to ensure quality data management, data checks including range checks, sampling data, and manual inspection were used regularly.

3.7. Missing Data and imputation

The physical activity questions included missing data for many fields. There was also inconsistency in the reporting of information. For example, some subjects provided information about both the number of minutes exercised per week and the number of hours exercised per week. Prior to computing the physical activity scores, the missing data were examined and imputation performed to improve data quality. The following material will illustrate the process employed, using walking in the age interval 20-29 as a case study. A similar process was applied to all activities and age intervals.

A cross tabulation table was created to determine the frequency and pattern of ‘missing’ data for physical activity variables. A representative table of these patterns is shown in Appendix 2, which provide a full list of missing physical activity patterns for walking in the age interval 20-29. Nineteen distinct patterns were identified. The final column in the table indicates how missing data or data errors were handled.

Four of the patterns (involving 1,131 of the 1,395 subjects) provided full data and did not require imputation. Fifty-three of these subjects had provided both minutes and hours of activities per week but the former was always 60 times the later suggesting a duplication rather than a reporting error.

For the remaining patterns, a series of assumptions were made for each missing pattern, in order to impute values that were missing among the physical activity data. In order to derive MET-hours per week, the following variables were required: activity (yes/no), hours per week (or minutes per week), months per year and number of years. If data on only one of the required variables were missing, then we imputed a value for the missing variable. However, if more than one variable required to derive MET-hours/week was missing, then MET-hours per week was assigned a value of missing for that activity.

One group of participants failed to provide information for any of the required variables, including no indication whether they did the activity. We assumed that they had not done the activity but neglected to check the ‘never’ response; we imputed ‘not done’ for this activity. A second group claimed to do the activity but gave no further information; we also imputed ‘not done’ in this case. Otherwise, imputations were made for missing data where only one variable was missing, or where there were clear errors. Hours per week were imputed using the median value among non-missing hours per week. Months per week and number of years were imputed

using mean values for subjects reporting a value. Further details are contained in Appendix 2. Chapter 4 lists the proportion of missing physical activities by activity for each age period.

Following imputation, it was observed that some individuals had missing physical activity data across all physical activities for one or more age periods. The decision was made to keep these observations and to treat these subjects as not having done these activities.

For the age period 20-29, there were 52 (3.7%) observations that had imputed values for each of the eight physical activities. Less than 1% of participants had imputed values for nine or more physical activities. Approximately 75% of the participants had no imputed values for any of the physical activities.

Similar results were found for imputations during the 30s, with 60 participants (4.3%) having imputed values for each of eight physical activities. The number increased to 76 (5.4%) with imputed values for all closed-ended physical activities during the 50s. After a cross-tabulation analysis, there were only 27 observations that had missing physical activity values for all eight closed-ended physical activities consistently across each age period. Once again, these 27 participants were assumed to have not participated in any activities across their lifetime and imputations to reflect this were made.

3.8. Statistical Analyses

Unconditional logistic regression models were used to estimate the association between CRC and physical activity during each age period and across the lifetime. All analyses were conducted using two models: age and sex-adjusted models and fully adjusted models that included all covariates in model. Analyses produced odds ratios (OR) and corresponding 95% confidence intervals associated with CRC. P-values <0.05 were considered statistically

significant. Subjects who reported no moderate/vigorous physical activity served as the reference group for all analyses

Physical activity as estimated by MET-hours per week was analyzed for each age period separately, as well as for the average activity. Sub-group analyses were performed to determine the association between physical activity and CRC by sex. A separate analysis was done to examine the relationship with colon cancer, excluding rectal cancer.

Goodness of fit was assessed using the Hosmer-Lemeshow test. This test measures how well the model describes the response variable by investigating how close the predicted values are to the observed values (Williams, 2011). P-values > 0.1 indicate non-significance of departure from adequate fit and are evidence of an acceptable model fit.

The statistical software package SAS (version 9.3; SAS Institute Inc., Cary, North Carolina, USA) was used for all analyses, mainly using the procedure PROC LOGISTIC.

3.9. Ethical approval

Ethics approval for the NFCCR study was originally obtained from the Research Ethics Board of the Memorial University of Newfoundland, and all patients or their proxies provided informed consent. Ethics approval for the current study, protocol #20120291-01H (approved until November 22, 2016), which utilized secondary data, was obtained from The Ottawa Hospital Research Ethics Board.

CHAPTER 4: RESULTS OF ANALYSIS OF POPULATION-BASED CASE-CONTROL DATA FROM NEWFOUNDLAND AND LABRADOR

1. Participant characteristics

A total of 1395 participants (692 cases and 703 controls) were included in the current study. The demographic and various lifestyle characteristics of the participants are presented in Table 4. Cases and controls were frequency matched on age and sex. Cases were slightly older than controls. The mean age for cases was 62.9 (SD=9.0) compared to 60.7 (SD=9.2) for controls. A total of 1258 participants (90.2%) were 50 years or older. More than half of the cases (60.3 %) and controls (59.0%) were men. Among cases, 449 (69.1%) had been diagnosed with colon cancer while 204 (30.9 %) had been diagnosed with rectal cancer (Table 5). The proportion of cases with distal colon cancer (i.e., descending and sigmoid colon) was lower compared to those with proximal colon cancers (i.e., ascending, hepatic flexure, cecum, and transverse): 39.3% compared to 55.0% of all colon cancers.

BMI estimates were obtained for two age windows: two years prior to the date of the questionnaire (recent) and also at age 20 as recalled by the participants. BMI estimates were missing for 75 subjects for recent BMI and for 127 subjects for BMI at the age of 20 years. The mean recent BMI for cases was 27.8 kg/m² (SD=4.8), compared to 27.3 kg/m² (SD=4.6) for controls. The mean BMI at the age of 20 for cases was 22.6 kg/m² (SD=3.5), compared to 22.2 kg/m² (SD=3.2) for controls. Based on recent BMI, only 28.9 % of cases and 30.4 % of controls were categorized as normal or underweight, while a total of 41.2 % of cases and 46.5 % of controls were categorized as overweight. This reflects an increase in BMI from the age of 20

Table 4. Participant characteristics, Newfoundland CRC Study 1999-2003 (n=1395)

	Cases (n=692)		Controls (n=703)	
Age (mean, SD)	62.9	9.0	60.7	9.2
	No.	%	No.	%
Sex				
women	275	39.7	288	40.9
men	417	60.3	415	59.1
BMI (2 years prior to reference date)¹				
<25.00	187	28.9	205	30.4
25.00 - 30.00	266	41.2	314	46.5
>30.00	192	29.8	156	23.1
missing	47		28	
BMI (at age 20-29)¹				
<25.00	481	78.5	532	81.2
25.00 - 30.00	108	17.6	111	16.9
>30.00	24	3.9	12	1.8
Missing	79		48	
Smoking status²				
Never	197	28.9	262	38.5
Former	347	50.9	329	47.4
Current	138	20.2	103	14.8
Missing	10		9	
Drinking alcohol³				
lifetime non-drinker	293	35.8	240	34.9
ever (during lifetime)	428	64.2	447	65.1
Missing	25		16	
Regular folic acid or folate pills use ⁴				
No	634	94.3	647	94.0
Yes	38	5.6	41	5.9
Missing	20		15	
Regular aspirin use ⁴				
No	497	73.4	477	68.2
Yes	180	26.6	222	31.8
Missing	15		4	
Regular calcium supplement use ⁴				
No	589	86.5	548	78.6
Yes	92	13.5	149	21.4
Missing	11		6	
Diabetes mellitus				
No	545	78.9	602	86.7
Yes	145	21.0	92	13.3
Missing	2		9	

Table 4. Participant characteristics (Cont'd)				
	No.	%	No.	%
Inflammatory Bowel Disease (IBD) ⁵				
No	652	97.3	659	97.8
Yes	18	2.7	15	2.2
Missing	22		29	
Ever had FOBT, sigmoidoscopy, or colonoscopy				
No	20	2.9	338	50.7
Yes	662	97.1	328	49.2
Missing	10		37	
Familial adenomatous polyposis (FAP)				
No	623	99.2	668	99.8
Yes	5	0.8	1	0.15
Missing	64		34	

¹ BMI classifications: underweight/normal weight, overweight, obese; self-reported weights: 2 years prior to reference date, and during their 20s

² Never smoked defined as never smoked at least 1 cigarette/day for 3 months; current= smoking 2 years prior to questionnaire date

³ Ever drank beer, wine, sake, or spirits/liquor during 20s, 30-40s, or since turning 50s at least once/week for a minimum of 6 months;

⁴ Regular = at least twice a week for more than a month

⁵ Crohn's disease or ulcerative colitis

† Age and sex-adjusted odds ratio (OR)

where the prevalence of being 'overweight' was 23.6 % and 29.9 % for cases and controls, respectively.

The majority of participants reported having smoked at least one cigarette a day for at least 3 months or longer (71.1% of cases and 62.2% of controls). A higher proportion of controls reported never smoking (38.5 %) compared to cases (28.9%). A total of 50.9% of cases and 47.4% controls were classified as 'former smoker'. Fewer participants were categorized as current smokers; only 20.2% cases and 14.8% controls reported that they had smoked one or more cigarettes/day two years prior to interview. When smoking was categorized as never, former or current smokers, there were missing data for 10 cases and 9 controls.

Alcoholic beverages were consumed at least once a week for 6 months or longer by 64.2% of cases and 65.1% of controls at some point from age 20 to the time period two years

Table 5. Colon and rectal malignant neoplasm distribution by subsite (n=653) ¹²

	No. of Cases ³	Percentage (%)
Colon cancer subsites		
Appendix	1	0.2
Cecum	114	17.5
Ascending colon (right colon)	56	8.6
Hepatic flexure	20	3.1
Transverse colon	56	8.6
Splenic flexure	19	2.9
Descending colon (left colon)	34	5.2
Sigmoid colon	144	22.0
Other colon/large intestine, unspecified	5	0.7
Rectal cancer subsites		
Recto-sigmoid junction	2	0.3
Rectum	202	30.9
Total		
Colon malignant neoplasms	449	69.1
Rectal malignant neoplasm	204	30.9

¹ Based on ICD9 codes and excludes benign carcinoid tumor of rectum, malignant carcinoid tumor of rectum, benign carcinoid tumor of colon, malignant carcinoid tumor of colon

² Additional tumors were excluded following original tumor ID identification and diagnosis date

³ Total numbers exclude 39 cases with missing ICD9 codes

prior to interview. During the age period of 20-29, 53.1% of cases and 55.4% of controls reported alcohol intake (results not included in table). A similar proportion reported alcohol intake during their 30s and 40s (56.7% in cases and 56.9% in controls). After age 50, approximately 50% of cases and controls reported drinking alcohol. There were 25 cases and 16 controls with missing lifetime drinking data.

The proportion of IBD (Crohn's disease and ulcerative colitis), was low for both cases (2.7%) and controls (2.4%). Cases were more likely to have diabetes than controls (21.8% and 13.3%, respectively). Controls were more likely to take aspirin (at least twice a day for one month of more) (31.8% vs. 26.6%), and calcium supplementation (21.4% vs. 13.5%) than cases. Few cases (5.6%) and controls (5.9%) reported that they took folic acid or folate regularly.

Only 5 cases and 1 control reported that a physician had told them that they had FAP. Among the cases, the mean age of diagnosis was 45.2, with a range of 31-64, and 3 of the 5 cases were female. The one control was diagnosed at 66 years and was male.

2. Physical activity: Missing Values and Imputation

2.1. Early adulthood (20s)

As a result of 'missing' values or data errors, imputations were made for walking (n=218), jogging (n=97), running (n=85), biking (n=124), swimming (n=117), ball sports (n=101), tennis (n=85), and aerobics (n=119). Among the closed-ended physical activities during the participant's 20s, walking included the most missing values and data errors or inconsistencies. Imputations were also made for up to 6 other opened-ended physical activities: first activity listed (n=69), second (n=37), third (n=10), fourth (n=7), fifth (n=1), and the sixth (n=1) activity listed.

These open- and closed-ended physical activity variables were summed together to yield an average MET-hours score during their 20s. When each of the closed-ended activities were summed together to produce a total closed-ended MET-hour per week score, 68 subjects had missing data from at least one the closed-ended physical activities during their 20s which precluded computation of a combined activity score. Similarly, the open ended responses were summed to produce a combined score. There were less missing scores from open-ended physical activities (n=24), after imputation and summation of all 6 variables. Following this process, there were 80 participants with missing data for total MET-hours/week during the 20s.

2.2. Mid-adulthood (30-40s)

A similar pattern for missing results was found among physical activity variables during the participant's 30-40s. Following the summation of the open and close-ended physical activity MET-hours/week scores during the 30-40s, there were 81 participants with missing data.

2.3. Late adulthood (since turning 50)

Once again, walking had the most missing values or discrepancies compared to any other activity. There were 65 participants over age 50 with missing data when close and open-ended physical activity MET-hours/week were summed together.

2.4. Lifetime missing patterns

When all age periods (following imputations) were combined, there were 149 missing values for the lifetime average MET-hours/week (Table 6).

3. Descriptive statistics and distribution of recreational physical activities per age period

The distribution of recreational physical activities during the participant's 20s, 30-40s, and since turning 50 is presented in Table 7. Appendix 3 demonstrates radar plots representing the distribution of physical activities for each age period. These graphs demonstrate the most common recreational physical activities reported from the list provided in the PHQ by age period (i.e., close-ended physical activities). The graphs demonstrate walking as the most common activity reported in each age period. In each radar plot, each 'web' represents a single observation. Thus, if majority of the participants report walking as their most common activity, the graph will generate a direction towards that activity.

Table 6. Number of participants who were active, non-active, or had missing average MET-hours per week

	Inactive (0 MET-hrs/wk)[§]	Active (>0 MET-hrs/wk)	Sample size[†]	Missing[*]
Age range				
Early adulthood: (20-29)	352	963	1315	80
Mid-adulthood (30-40s)	403	911	1314	81
Late adulthood (50 +)	385	808	1193 [‡]	65
Lifetime (20+)	209	1037	1246	149

* Also, includes 1 subject who reported >168 hours of activity per week during their 30-40s.

§ '0 MET-hours/wk implies that the subject reported no participation in any of the 8 specific activities and did not report an optional activities.

‡ Excludes 137 subjects who were younger than 50 on the data of interview.

† Sample size available for analyses after imputations. Excludes missing data.

3.1. Early adulthood (20s)

The average MET-hours per week for each age period and across the lifetime are presented in Table 8. A total of 352 participants (26.8%) did not participate in any moderate or vigorous activities during that age period. The proportion of individuals who were non-active was higher in cases (30%) than in controls (24%). Among individuals who reported participating in any moderate or vigorous physical activity, the mean MET-hours per week during their 20s was 39.8 (SD=53.8), which would be equivalent to walking for 11.3 hours per week on average, or jogging for 5.6 hours per week. The mean MET-hours per week for cases was 41.8 (SD=56.4) compared to 38.0 (SD=51.3) for controls. A total of 80 participants had missing total MET-hours/week during their 20s and were excluded, resulting in a total of 1315 participants with MET-hours per week data.

The most commonly reported physical activity during early adulthood (20s) was walking, with nearly 62% of participants reporting that they walked regularly. The second most common moderate or vigorous recreational physical activity was hunting (15%), while biking followed closely with 14% participation.

Table 7. Distribution of the most common reported recreational physical activities across the lifetime ¹

	Age 20-29	Age 30-49	Age 50 +
	No. (%)	No. (%)	No. (%)
Closed ended questions			
Walking	862 (61.8)	809 (57.9)	777 (61.7)
Biking	196 (14.0)	138 (9.9)	97 (7.7)
Swimming	188 (13.4)	126 (9.0)	62 (4.9)
Aerobics/calisthenics	146 (10.5)	124 (8.9)	45 (3.5)
Football	145 (10.4)	75 (5.4)	21 (1.7)
Jogging	86 (6.2)	59 (4.2)	13 (1.0)
Running	63 (4.5)	40 (2.9)	8 (0.6)
Open-ended questions			
Hunting	208 (14.9)	201 (14.4)	176 (11.6)
Hockey	169 (12.1)	60 (4.3)	10 (0.7)
Skating	145 (10.4)	66 (4.7)	30 (2.3)
Fishing	43 (3.0)	39 (2.8)	23 (1.8)
Skiing	42 (3.0)	49 (3.5)	27 (2.1)
Cutting wood	34 (2.4)	90 (6.4)	30 (2.3)
Softball	34 (2.4)	26 (1.8)	N/A
Curling	14 (1.0)	14 (1.0)	8 (0.6)
Gardening	N/A	N/A	35 (2.8)
# subjects	1395	1395	1258

¹ Categories non-mutually exclusive (i.e. participants may perform >1 activity)

3.2. Mid-adulthood (30-40s)

A total of 403 participants (30.7%) reported no moderate or vigorous physical activity during this age period compared to 26.8% in their 20s. More cases (33%) than controls (28%) were non-active. Among individuals who were active during their 30-40s, the mean MET-hours per week was 27.1 (SD=39.5), which would be equivalent to 7.7 hours per week of walking or 3.8 hours per week of jogging. Among active participants, cases had a higher mean MET-hours/week score than controls (32.2 vs. 22.4, respectively). A total of 81 participants had missing total MET-hours per week. One participant had reported walking for more than 168

Table 8. Average MET-hours per week per life period among active participants

		All	Cases	Controls
	Sample size	Mean (SD) (for people with >0 MET-hrs/week)		
Early adulthood (20-29)	1395	39.8 (53.8)	41.8 (56.4)	38.0 (51.3)
Mid-adulthood (30-40s)	1394	27.1 (39.5)	32.2 (47.0)	22.4 (30.4)
Late adulthood (50 +) ^a	1193	23.3 (31.6)	25.6 (35.2)	21.4 (27.9)
Lifetime (20+) [†]	1246	25.0 (33.3)	27.6 (38.2)	22.8 (28.2)

^a excludes individuals who are less than 50 years of age (n=1258);

[†]based on average MET-hours/week values;

SD= standard deviation

hours per week during their 30-40s and was excluded, leaving 1314 participants with MET-hours per week data. During the participant's 30-40s, walking and hunting were also the most commonly performed, but with ~3% fewer participants walking compared to during their 20s.

3.3. Late adulthood (since turning 50) MET-hours per week

A total of 384 (32.2%) of participants did not report engaging in moderate or vigorous recreational physical activities since their 50s. The mean MET-hours per week among people who participated in some moderate or vigorous physical activity since turning 50 was lower than any other age period (23.3, SD=31.6), which is equivalent to walking for a total of 6.6 hours or jogging regularly for 3.3 hours per week. Active cases had a higher MET-hours/week score than active controls (25.6 vs. 21.4). More cases (35.7%) were non-active than controls (28.7%).

There was 65 participants with missing MET-hours per week from the 1258 participants who were 50 years or older, resulting in 1193 participants with MET-hours per week data.

Walking remained the most common activity reported from age 50+, with 62% of participants regularly walking. However, for the rest of the activities listed in the open-ended portion of the questionnaire, there was a considerable change in the type of activities. For

example, more participants engaged in gardening and curling in their late adulthood, and fewer participants reported playing sports such as hockey.

3.4. Lifetime MET-hours per week

A total of 209 (16.8%) did not report any moderate or vigorous physical activities at any point in their adult lifetime. The lifetime mean MET-hours per week was 25.0 (SD=33.3) and the median MET-hours per week was 13.9 among participants who were active. More cases (20.1%) than controls (13.7%) did not engage in any physical activities over their adult lifetime. However, among those who were active, the lifetime MET-hours/week score was higher among cases than controls, 27.7 vs. 22.8 respectively.

3.5. Overall comments

These results suggest cases were more likely to be non-active than controls, but were also more likely to have higher energy expenditure than controls among those who were active. Overall, the mean values for physical activity, as measured by MET-hours per week, decreased with age when comparing early adulthood with older adulthood.

4. Association of Physical Activity and Colorectal Cancer Risk

The association between physical activity and the risk of CRC was estimated using multivariate logistic regression models for each age period and across the lifetime (Tables 9-12). Physical Activity was categorized into five levels for the analysis. For all analyses, '0' MET-hours/week was the reference group. Individuals with >0 MET-hours per week were categorized into quartiles, based on the distribution of physical activity in the cases. All models were interpreted as providing a good fit, based on the Hosmer-Lemeshow test (p value>0.05).

Results are present from two analytic models. The first was adjusted for only the matching factors (age and sex). The second provided for a full adjustment for the matching factors and the selected covariates. The analyses were conducted separately using physical activity from each age range as the primary predictor variable. A fourth analysis was conducted based on the lifetime physical activity estimates. For each of these four analyses, subjects who were missing data on any of the variables included the fully adjusted model were excluded from both the age-sex adjusted and the fully adjusted models.

4.1. Early adulthood (20's)

The models were restricted to 1103 participants, following the exclusion of 315 participants with missing physical activity (MET-hours/week) or missing covariates from the fully-adjusted model (Table 9). In neither model was there a significant relationship between physical activity and risk of colorectal cancer ($p=0.28$ for the age-sex adjusted model and $p=0.42$ for the fully adjusted model). In the age and sex adjusted model, there was a non-significant risk reduction in CRC among those who participated in physical activity up to an average of 52.5 MET-hours per week. However, the risk reductions associated with physical activity were attenuated when adjusted for potential confounders in the fully adjusted model compared to the age and sex-adjusted only model. There was a non-significant elevation in the OR for the highest physical activity level (over 52.2 MET-hr/week) which was slightly stronger in the fully adjusted model (OR: 1.23 (95% CI: 0.83-1.84) than in the age-sex adjusted model (OR=1.18 (95% 0.80-1.75)). 1.18 (0.80-1.75) There is no evidence for a trend towards a higher protective effect for higher levels of physical activity.

The lack of significance may reflect a small sample size: only 101 cases and 92 controls reported to have had an average of 52 MET-hours per week. It may also reflect a relatively low

level of physical activity for the highest activity group: an average of 52.5 MET-hours per week would be equivalent to accumulating an average of 7 hours of jogging per week, or 14 hours of walking per week, or a combination of activities.

Four covariates were significantly independently associated with CRC: BMI (weight based on their 20s), smoking, regular aspirin use, and regular calcium supplementation use. Compared to being normal/underweight (BMI <25.0 kg/m²), being overweight (BMI 25-30 kg/m²) was associated a non-significant 20% increase in risk of CRC while being obese (BMI>30.0 kg/m²) was associated with a significant nearly 3-fold increase in CRC risk when compared to normal/underweight participants. Smoking was also significantly associated with CRC risk when compared to never-smokers (OR for former smokers: 1.55, 95% CI: 1.16-2.08); OR for current smokers: 1.87, 95% CI: 1.28-2.73). Furthermore, regularly taking calcium supplements and aspirin both significantly decreased the risk of CRC by about 40%.

Table 9. Associations between CRC, recreational physical activities and other covariates reported during the age period: 20-29* (n=1103)

	Cases (n=519)		Controls (n=584)		Age and sex-adjusted OR	Fully adjusted OR†
	No.	(%)	No.	(%)	OR (95% CI)	OR (95% CI)
Physical activity (average MET-hours/week)[‡]						
0	127	24.7	132	22.6	Ref.	Ref.
>0 to 9.5	92	17.7	129	22.0	0.78 (0.54-1.13)	0.83 (0.57-1.20)
>9.5 to 23.5	95	18.3	104	17.8	0.99 (0.68-1.45)	1.04 (0.71-1.53)
>23.5 to 52.5	104	20.0	127	21.7	0.86 (0.60-1.23)	0.95 (0.65-1.37)
>52.5	101	19.5	92	15.7	1.18 (0.80-1.75)	1.23 (0.83-1.84)
Covariates						
BMI (age period: 20-29)						
<25.0	406	78.2	478	81.8	Ref.	Ref.
25.0 to 30.0	90	17.3	95	16.3	1.19 (0.86-1.65)	1.20 (0.86-1.68)
>30.0	23	4.4	11	1.9	3.03 (1.43-6.38)	2.95 (1.36-6.42)
Smoking Status						
Never	148	28.5	220	37.7	Ref.	Ref.
Former	272	52.4	279	47.8	1.46 (1.10-1.93)	1.55 (1.16-2.08)
Current	99	19.0	85	14.5	1.86 (1.29-2.68)	1.87 (1.28-2.73)
Drinking alcohol (age period: 20-29)						
Never	251	48.4	259	44.9	Ref.	Ref.
Ever	268	51.6	322	55.1	0.95 (0.71-1.26)	0.89 (0.66-1.21)
Regular folic acid/folate use						
No	489	94.2	544	93.2	Ref.	Ref.
Yes	30	5.8	40	6.8	0.89 (0.55-1.47)	1.02 (0.60-1.70)
Regular aspirin use						
No	385	74.2	396	67.8	Ref.	Ref.
Yes	134	25.8	188	32.2	0.67 (0.51-0.88)	0.63 (0.47-0.83)
Regular calcium use						
No	444	85.5	462	79.1	Ref.	Ref.
Yes	75	14.4	122	20.9	0.56 (0.40-0.79)	0.61 (0.43-0.87)
Diabetes						
No	413	79.6	509	87.1	Ref.	Ref.
Yes	106	20.4	75	12.9	1.55 (1.12-2.17)	1.45 (1.03-2.05)
Inflammatory Bowel Disease (IBD)						
No	506	97.5	570	97.6	Ref.	Ref.
Yes	13	2.6	14	2.4	1.09 (0.50-2.34)	1.29 (0.58-2.85)

†fully adjusted logistic regression model was adjusted for: age, sex, BMI (self-reported weight from their 20s), alcohol (ever 1xweek for ≥ 6 months/never during their 20s), regular aspirin use, calcium use and folate use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former)

[‡]no activity group was the reference; remaining subjects were classified into quartiles based on the distribution of MET-hours among cases; significant values indicated in bold

*Sample size was the same for both analyses; 315 participants were excluded due to missing data.

4.2. Mid-adulthood (30-40s)

Analyses were restricted to 1139 participants following exclusion of participants with missing MET-hours per week and covariates during this age period (Table 10). In the age and sex adjusted model, there was a borderline significant relationship between physical activity and risk of colorectal cancer ($p = 0.079$ for the age-sex adjusted model). In the fully adjusted model, the effect was not significant ($p = 0.1166$ for the fully adjusted model). In the age-sex adjusted model, there was a non-significant increase in CRC risk among those who participated in the low and middle physical activity groups up to an average of 35.6 MET-hours per week. However, the risk reductions associated with physical activity were attenuated when adjusted for potential confounders in the fully adjusted model compared to the age and sex-adjusted only model. There was a non-significant elevation in the OR for the highest physical activity level (over 35.6 MET-hr/week) compared to 0 MET-hrs/week which was stronger in the fully adjusted model (OR: 1.37, 95% CI: 0.93-2.03). Once again, there is no evidence for a trend towards a higher protective effect with higher levels of physical activity.

The covariates that were significantly associated with CRC during the participant's 30s and 40s include age, smoking, regular aspirin and calcium (pill) use, and diabetes. Smoking was also significantly associated with CRC risk (OR for current smokers: (OR=2.02, 95% CI: 1.38, 2.95) compared to never smokers. Diabetes was associated with a significant 53% increased risk of CRC (OR: 1.57 (95% CI: 1.12-2.20). Finally, regular calcium and aspirin use resulted in significant risk reductions of 41% and 35%, respectively.

Table 10. Associations between CRC and recreational physical activities reported during the age period: 30-49 (n=1139)*

	Cases (n=552)		Controls (n=587)		Age and sex-adjusted OR	Fully-adjusted OR†
	No.	(%)	No.	(%)	(95% CI)	(95% CI)
Physical activity (average MET-hours/week)¹						
0	166	30.0	153	26.0	Ref.	Ref.
>0 to 5.6	95	17.2	123	20.9	0.79 (0.56-1.14)	0.88 (0.60-1.27)
>5.6 to 15.9	94	17.0	131	22.3	0.70 (0.49-0.99)	0.79 (0.55-1.13)
>15.9 to 35.6	99	17.9	101	17.2	0.94 (0.66-1.35)	1.03 (0.71-1.48)
>35.6	98	17.7	79	13.5	1.20 (0.83-1.76)	1.37 (0.93-2.03)
Covariates						
BMI (<2 years prior to reference date)						
<25.0	154	27.9	174	29.6	Ref.	Ref.
25.0 to 30.0	228	42.1	274	46.7	0.93 (0.69-1.23)	0.89 (0.67-1.20)
>30.0	166	30.0	139	23.7	1.41 (1.02-1.95)	1.29 (0.92-1.80)
Smoking Status						
Never	153	27.7	221	37.6	Ref.	Ref.
Former	290	52.5	271	48.2	1.44 (1.11-1.93)	1.50 (1.12-2.01)
Current	109	19.7	83	14.1	2.06 (1.43-2.96)	2.02 (1.38-2.95)
Drinking alcohol (age period: 30-49)						
Never (30/40s)	243	44.0	260	44.2	Ref.	Ref.
Ever	309	55.9	327	55.7	1.09 (0.84-1.43)	1.00 (0.75-1.34)
Regular folic acid/folate use						
No	520	94.2	551	93.9	Ref.	Ref.
Yes	32	5.8	36	6.1	1.00 (0.61-1.65)	1.14 (0.68-1.93)
Regular aspirin use						
No	404	73.2	400	68.1	Ref.	Ref.
Yes	148	26.8	187	31.9	0.71 (0.55-0.93)	0.65 (0.49-0.86)
Regular calcium use						
No	474	85.9	463	78.8	Ref.	Ref.
Yes	78	14.1	124	21.2	0.54 (0.38-0.75)	0.59 (0.42-0.85)
Diabetes						
No	437	79.2	513	87.4	Ref.	Ref.
Yes	115	20.8	74	12.6	1.62 (1.17-2.25)	1.57 (1.12-2.20)
Inflammatory Bowel Disease (IBD)						
No	539	97.6	573	97.6	Ref.	Ref.
Yes	13	2.4	14	2.4	1.03 (0.48-2.23)	1.21 (0.55-2.67)

†Fully-adjusted logistic regression model, adjusted for age, sex, BMI (weight 2 years < questionnaire), alcohol (ever 1/week for ≥ 6 months/never in their 30-40s), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former); significant values indicated in bold

¹ Based on the univariate distribution of MET-hours among cases

*Sample size was the same for both analyses; 278 participants were excluded due to missing data

4.3. Late adulthood (since their 50s)

Analysis of this exposure was restricted to participants who were 50 years or older, leading to a lower sample size. Analyses were restricted to 1020 participants following exclusion of subjects with missing MET-hours per week and covariates (Table 11). In neither model was there a significant relationship between physical activity and risk of colorectal cancer ($p = 0.13$ for the age-sex adjusted model and $p = 0.22$ for the fully adjusted model). In the age-sex adjusted model, there was a non-significant risk reduction in CRC risk among those who participated in middle physical activity group (an average of 30.2 MET-hours per week). Once again, the risk reductions associated with physical activity were attenuated when adjusting for potential confounders in the fully adjusted model compared to the age and sex-adjusted only model. Similar to other age periods, there was a non-significant elevation in the OR for the highest physical activity level (over 30.2 MET-hr/week) compared to 0 MET-hrs/week which was stronger in the fully adjusted model (OR: 1.24, 95% CI: 0.83-1.84). There is no evidence for a trend towards a higher protective effect with higher levels of physical activity.

The covariates that were significantly associated with CRC during the 50s were smoking, regular aspirin use, regular calcium supplement intake, and diabetes. Calcium and aspirin had similar effects to other age periods. Like all other age periods, smoking was also significantly associated with CRC risk when compared to never-smokers (OR for former smokers: 1.44, 95% CI: 1.06-1.95; OR for current smokers: 1.69, 95% CI: 1.13-2.54). This was the only age period BMI was not significantly associated with CRC in the fully adjusted model.

Table 11. Associations between CRC and recreational physical activities reported during the age period: 50+ (n=1020)*

	Cases (n=500)		Controls (n=520)		Age and sex-adjusted OR	Fully-adjusted OR†
	No.	(%)	No.	(%)	(95% CI)	(95% CI)
Physical activity (average MET-hours/week)¹						
0	150	30.0	134	25.7	Ref.	Ref.
>0 to 6.5	90	18.0	98	18.8	0.83 (0.57-1.20)	0.90 (0.61-1.33)
>6.5 to 16.5	83	16.6	114	21.9	0.64 (0.44-0.93)	0.72 (0.49-1.05)
>16.5 to 30.2	87	17.4	95	18.3	0.83 (0.57-1.21)	0.94 (0.63-1.39)
>30.2	90	18.0	79	15.2	1.05 (0.71-1.55)	1.22 (0.81-1.82)
Covariates						
BMI (<2 years prior to reference date)						
<25.0	136	27.2	160	30.8	Ref.	Ref.
25.0 to 30.0	214	42.8	247	47.5	0.97 (0.72-1.31)	0.94 (0.69-1.28)
>30.0	150	30.0	113	21.7	1.63 (1.16-2.30)	1.43 (1.00-2.05)
Smoking Status						
Never	140	28.6	194	38.0	Ref.	Ref.
Former	88	18.0	73	14.4	1.48 (1.10-1.97)	1.44 (1.07-1.95)
Current	261	53.4	243	47.6	1.76 (1.19-2.58)	1.69 (1.13-2.54)
Drinking alcohol (since turning 50)						
Never (30/40s)	252	50.4	268	51.5	Ref.	Ref.
Ever	248	49.6	252	48.5	1.06 (0.82-1.39)	1.03 (0.78-1.37)
Regular folic acid/folate use						
No	474	94.8	486	93.5	Ref.	Ref.
Yes	26	5.2	34	6.5	0.86 (0.51-1.46)	0.98 (0.56-1.70)
Regular aspirin use						
No	357	71.4	348	66.9	Ref.	Ref.
Yes	143	28.6	172	33.1	0.75 (0.57-0.98)	0.69 (0.52-0.93)
Regular calcium use						
No	427	85.4	400	76.9	Ref.	Ref.
Yes	73	14.6	120	23.1	0.52 (0.37-0.75)	0.59 (0.41-0.85)
Diabetes						
No	384	76.8	447	85.9	Ref.	Ref.
Yes	116	23.2	73	14.1	1.68 (1.21-2.34)	1.59 (1.13-2.24)
Inflammatory Bowel Disease (IBD)						
No	490	98.0	507	97.4	Ref.	Ref.
Yes	10	2.0	13	2.6	0.88 (0.38-2.05)	1.10 (0.47-2.63)

‡Multivariate logistic regression, adjusted for age, sex, BMI (weight 2 years prior to questionnaire), alcohol (ever 1xweek for ≥6 months/never since turning 50), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), smoking (never/current/former)

¹ Based on the univariate distribution of MET-hours among cases; significant values indicated in bold

**Sample size was the same for both analyses; 258 participants were excluded due to missing data

4.4. Lifetime (average MET-hours/week since their 20s)

There was weak evidence for a protective effect of physical activity on CRC risk but the effect was not significant (p-value = 0.26) (Table 12). All OR estimates were under 1.0 although none achieved statistical significance. There was no evidence of a trend for reduced risk with higher levels of physical activity. In fact, the fully adjusted odds ratio for the highest activity group (≥ 33.0 MET-hours/week) compared to 0 MET-hours/week was 0.99 (95% CI 0.64, 1.55). Risk reductions for CRC ranged between 13-31% among individuals who averaged 0-6, 6-14.7, and 14.7-32.0 MET-hours per week, respectively. However, these risk estimates were non-significant. The covariates that were significantly associated with CRC in this analysis were smoking, regular aspirin use, regular calcium supplement intake, and diabetes. Smoking was significantly associated with CRC risk when compared to never-smokers (OR for former smokers: 1.58, 95% CI: 1.17-2.15; OR for current smokers: 2.12, 95% CI: 1.44-3.12). Similar to the age period since turning 50, BMI was not significantly associated with CRC in the fully adjusted model.

4.5. Overall results for primary analysis

There were no significant associations between recreational physical activity at any age period or across the lifetime. There was a general tendency for mean MET-hours/week values to decrease with increasing age period, for both cases and controls. Overall, more cases reported being sedentary than controls. Among other covariates, smoking (former and current) was significantly associated with CRC at every age period and across the lifetime.

Table 12. Associations between CRC and reported average lifetime recreational physical activities (n=1075)*

	Cases (n=507)		Controls (n=568)		Age and sex- adjusted OR	Fully-adjusted OR†
	No.	(%)	No.	(%)	(95% CI)	(95% CI)
Physical activity (average lifetime MET-hours/week) ¹						
0	86	16.9	67	11.8	Ref.	Ref.
>0 to 6	98	19.3	131	23.5	0.60 (0.39-0.92)	0.63 (0.41-0.97)
6 to 14.7	102	20.1	136	23.9	0.60 (0.40-0.91)	0.67 (0.44-1.02)
14.7 to 33.0	110	21.7	123	21.6	0.73 (0.48-1.09)	0.80 (0.53-1.23)
>33.0	111	21.9	111	19.5	0.83 (0.54-1.27)	0.95 (0.61-1.46)
Covariates						
BMI (<2 years prior to reference date)						
<25.0	141	27.8	167	29.4	Ref.	Ref.
25.0 to 30.0	214	42.4	268	47.2	0.94 (0.69-1.26)	0.93 (0.68-1.26)
>30.0	152	29.8	133	23.4	1.42 (1.02-1.98)	1.29 (0.91-1.83)
Smoking Status						
Never	138	27.9	211	37.1	Ref.	Ref.
Former	269	53.0	276	48.6	1.48 (1.11-1.97)	1.58 (1.17-2.15)
Current	100	19.7	81	14.6	2.03 (1.40-1.97)	2.12 (1.44-3.12)
Drinking alcohol (lifetime)						
Never	183	36.4	191	33.6	Ref.	Ref.
Ever	324	63.6	377	66.4	0.98 (0.73-1.30)	0.89 (0.66-1.21)
Regular folic acid/folate use						
No	479	94.3	530	93.3	Ref.	Ref.
Yes	28	5.7	38	6.7	0.91 (0.54-1.50)	1.03 (0.60-1.76)
Regular aspirin use						
No	372	73.3	382	67.2	Ref.	Ref.
Yes	135	26.7	186	32.8	0.69 (0.53-0.91)	0.64 (0.48-0.85)
Regular calcium use						
No	437	86.5	450	79.2	Ref.	Ref.
Yes	70	13.5	118	20.8	0.56 (0.40-0.78)	0.56 (0.39-0.82)
Diabetes						
No	402	79.6	495	87.0	Ref.	Ref.
Yes	105	20.4	73	12.9	1.54 (1.10-2.16)	1.48 (1.04-2.12)
Inflammatory Bowel Disease (IBD)						
No	496	97.8	555	97.7	Ref.	Ref.
Yes	11	2.2	13	2.3	0.99 (0.44-2.24)	1.21 (0.52-2.82)

‡Fully-adjusted logistic regression model, adjusted for age, sex, BMI (weight 2 years prior to questionnaire), alcohol (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former)

¹ Based on the univariate distribution of MET-hours among cases

* Sample size was the same for both analyses; 344 participants were excluded due to missing data

5. Sex-specific analyses

The association between CRC and physical activity was assessed separately for men and women by sex for each age period and across the lifetime. In the fully-adjusted models for women, additional adjustment was made for women who ever had hormone replacement therapy (estrogen or progesterone).

Table 13. Associations between recreational physical activities performed during the age period: 20-29 and CRC among men (n=643)

Men (n=643)						
	Cases (n=302)		Controls (n=341)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	68	22.5	68	19.9	Ref.	Ref.
>0 to 9.5	40	13.2	68	19.9	0.60 (0.36-1.00)	0.61 (0.36-1.05)
>9.5 to 23.5	46	15.2	48	14.1	0.97 (0.57-1.65)	0.95 (0.55-1.64)
>23.5 to 52.5	62	20.5	79	23.2	0.79 (0.49-1.27)	0.91 (0.56-1.48)
>52.5	86	28.5	78	22.9	1.10 (0.70-1.75)	1.19 (0.74-1.90)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight at 20 yrs), alcohol during age period 20-29 (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former); significant values in bold

Table 14. Associations between recreational physical activities performed during the age period: 20-29 and CRC among women (n=437)

Women (n=431)						
	Cases (n=206)		Controls (n=231)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	56	27.2	61	26.4	Ref.	Ref.
>0 to 9.5	50	24.3	58	25.1	1.08 (0.63-1.85)	1.08 (0.60-1.93)
>9.5 to 23.5	47	22.8	54	23.4	1.08 (0.63-1.87)	1.08 (0.59-1.94)
>23.5 to 52.5	42	20.4	46	19.9	0.99 (0.56-1.74)	0.97 (0.53-1.76)
>52.5	11	5.3	12	5.2	0.96 (0.38-2.39)	0.89 (0.33-2.44)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight at 20 yrs), alcohol during age period 20-29 (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), HRT (yes/no), smoking (never/current/former); significant values in bold

5.1. Physical activity and CRC by sex during the age period: 20-29

In men, there was a non-significant inverse association between CRC and participation in physical activity up to an average of 52.5 MET-hours/week during their 20s, in the age-adjusted model. The risk reductions associated with physical activity were slightly attenuated when adjusted for potential confounders in the fully adjusted model compared to the age and sex-adjusted only model. There was a non-significant elevation in the OR for the highest physical activity level (over 52.5 MET-hr/week) compared to 0 MET-hrs/week which was stronger in the fully adjusted model (OR: 1.19, 95% CI: 0.74-1.90). For men, the highest physical activity group included 86 and 78 cases and controls, respectively.

In women, there was a lack of an association between CRC and participation in physical activity up to an average of 52.5 MET-hours/week during their 20s in both models. There was a non-significant decrease in the OR for the highest physical activity level (over 52.5 MET-hr/week) compared to 0 MET-hrs/week in the fully adjusted model (OR: 0.89, 95% CI: 0.33-2.44). The proportion of women who participated in the highest physical activity category was very low: 11 cases and 12 controls.

5.2. Physical activity and CRC by sex during the age period: 30-49

There was no trend observed for the association between physical activity and CRC among men or women with increasing MET-hours per week during the age period 30-49. Risk estimates were similar between similar in men and women when comparing highest physical activity group to non-active participants. For both men and women, there was a non-significant elevation in the OR for the highest physical activity level (over 35.6 MET-hr/week) compared to 0 MET-hrs/week which was stronger in the fully adjusted models and greater among men than women. The proportion of participants who engaged in the highest physical activity category

Table 15. Associations between recreational physical activities performed during the age period: 30-49 and CRC among men (n=679)

Men (n=679)						
	Cases (n=331)		Controls (n=348)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	94	28.4	92	26.4	Ref.	Ref.
>0 to 5.6	46	13.9	59	16.9	0.82 (0.50-1.34)	0.96 (0.58-1.58)
>5.6 to 15.9	52	15.7	68	19.5	0.77 (0.48-1.23)	0.87 (0.54-1.42)
>15.9 to 35.6	57	17.2	64	18.4	0.91 (0.57-1.45)	1.02 (0.63-1.65)
>35.6	82	24.8	65	18.7	1.27 (0.82-1.97)	1.53 (0.97-2.42)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight 2 yrs prior to reference date), alcohol during age period 30-49 (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former); significant values in bold

Table 16. Associations between recreational physical activities performed during the age period: 30-49 and CRC among women (n=437)

Women (n=437)						
	Cases (n=210)		Controls (n=227)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	66	31.4	59	25.9	Ref.	Ref.
>0 to 5.6	47	19.5	61	26.9	0.83 (0.48-1.42)	0.98 (0.55-1.72)
>5.6 to 15.9	41	19.5	60	26.4	0.69 (0.40-1.18)	0.79 (0.45-1.39)
>15.9 to 35.6	41	19.5	34	14.9	1.12 (0.93-2.00)	1.21 (0.65-2.23)
>35.6	15	7.1	13	5.7	1.02 (0.45-2.35)	1.22 (0.50-2.98)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight 2 yrs prior to reference date), alcohol during age period 30-49 (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), HRT (yes/no), and smoking (never/current/former); significant values in bold

was higher for men than women (82 cases and 65 controls vs. 15 cases and 13 controls, respectively).

Table 17. Associations between recreational physical activities performed during the age period: 50+ and CRC among men (n=573)

Men (n=573)						
	Cases (n=278)		Controls (n=295)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	87	29.2	79	26.8	Ref.	Ref.
>0 to 6.5	49	16.4	46	15.6	1.08 (0.65-1.80)	1.21 (0.71-2.05)
>6.5 to 16.5	39	13.1	58	19.7	0.66 (0.39-1.09)	0.74 (0.44-1.25)
>16.5 to 30.2	33	17.8	55	18.6	0.82 (0.51-1.32)	0.95 (0.58-1.56)
>30.2	70	23.5	57	19.3	1.26 (0.79-2.01)	1.47 (0.90-2.40)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight 2 yrs prior to reference date), alcohol during age period 30-49 (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), smoking (never/current/former); Significant values in bold

Table 18. Associations between recreational physical activities performed during the age period: 50+ and CRC among women (n=401)

Women (n=401)						
	Cases (n=191)		Controls (n=210)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	57	29.8	48	22.9	Ref.	Ref.
>0 to 6.5	40	20.9	52	24.8	0.64 (0.36-1.13)	0.76 (0.42-1.39)
>6.5 to 16.5	43	22.5	57	27.1	0.62 (0.36-1.09)	0.74 (0.41-1.34)
>16.5 to 30.2	34	17.8	32	15.2	0.94 (0.50-1.76)	1.09 (0.56-2.14)
>30.2	17	8.9	21	10.0	0.67 (0.31-1.42)	0.76 (0.34-1.69)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight 2 years prior to questionnaire), alcohol since 50 years (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former), HRT (yes/no); significant values in bold

5.3. Physical activity and CRC by sex during the age period: 50+

For the age period: ‘50 years and older’, there was no trend observed for the association between physical activity and CRC among men or women with increasing MET-hours per week. But for men, the highest physical activity group resulted in a non-significant increase in CRC

risk when comparing highest physical activity group to those non-active. When comparing the highest physical activity level (over 30.2 MET-hr/week) to the non-active group, the OR for women was 0.76 (95% CI: 0.34-1.69), whereas for men, the OR for this comparison was 1.47 (95% CI: 0.90-2.40). The proportion of participants who engaged in the highest physical activity category was higher for men than women (70 cases and 57 controls vs. 17 cases and 21 controls, respectively).

5.4. Lifetime physical activity and CRC by sex

The association between lifetime physical activity and CRC was stronger among women than for men (Table 19 and 20) although none of the ORs were statistically significant. The greatest difference between sexes was in the highest MET-hours per week quintile. Compared to 0 MET-hours per week, women who participated in 33.0 or more MET-hours per week had a non-significant 28% CRC risk reduction (OR: 0.58, 95% CI: 0.22-1.51). In contrast and much like the age period-specific analyses, men had a non-significantly increased risk of CRC when comparing the highest physical activity group to those who did not engage in any moderate or vigorous activities (OR: 1.12, 95% CI: 0.66-1.90). This may suggest some difference in effect among higher MET-hours per week when comparing men and women. However, the results were not statistically significant. The sample size for women in the highest physical activity category was very small (15 case and 18 controls)

Table 19. Associations between lifetime recreational physical activities and CRC among men (n=642)

Men (n=642)						
	Cases (n=301)		Controls (n=341)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	48	15.9	44	12.9	Ref.	Ref.
>0 to 6	46	15.3	60	17.6	0.71 (0.40-1.25)	0.74 (0.41-1.32)
6 to 14.7	49	16.3	71	20.8	0.65 (0.38-1.14)	0.77 (0.43-1.36)
14.7 to 33.0	66	21.9	75	21.9	0.81 (0.48-1.38)	0.91 (0.53-1.57)
>33.0	92	30.6	91	26.7	0.98 (0.58-1.59)	1.12 (0.66-1.90)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight 2 years prior to questionnaire), alcohol (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former); significant values in bold

Table 20. Associations between lifetime recreational physical activities and CRC among women (n=404)

Women (n=404)						
	Cases (n=191)		Controls (n=213)		Age-adjusted OR	Fully-adjusted OR [†]
	No.	%	No.	%		
Physical activity (MET-hours/week)						
0	32	16.7	22	10.3	Ref.	Ref.
>0 to 6	49	25.6	65	30.5	0.58 (0.29-1.13)	0.64 (0.31-1.29)
6 to 14.7	52	27.2	61	28.6	0.63 (0.32-1.22)	0.67 (0.33-1.36)
14.7 to 33.0	43	22.5	47	22.1	0.72 (0.36-1.45)	0.91 (0.43-1.93)
>33.0	15	7.5	18	8.4	0.54 (0.22-1.32)	0.58 (0.22-1.51)

[†]Fully-adjusted logistic regression model, adjusted for age, BMI (weight 2 years prior to questionnaire), alcohol (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate pill/tablet use (at least twice a week for 1 month) (yes/no), IBD (yes/no), HRT (ever/never) and smoking (never/current/former); Significant values in bold

6. Lifetime physical activity and colon cancer risk

The analyses were repeated with the case group restricted to people with colon cancer (as distinct from rectal cancer). Following exclusion of participants with rectal cancer and those

with missing data for any of the variables in the fully adjusted model, the sample size for these analyses was 865. The results are presented only for estimated lifetime physical activity.

A pattern compatible with overall risk reduction associated with physical activity was more apparent than for the lifetime analysis with CRC as disease end-point (Table 21), but was not statistically significant. In particular, there was a non-significant inverse association between participants who participated in the highest physical activity quartile (≥ 28.8 average lifetime MET-hours/week) compared to those who did not engage in any moderate or vigorous physical activity (OR: 0.84, 95% CI 0.51, 1.38) from the fully-adjusted model. Age and sex-adjusted ORs were generally lower compared to the fully-adjusted models, suggesting there is evidence of confounding. Other covariates that were significantly associated with colon cancer include smoking (current and former), regular aspirin and calcium use, and diabetes.

7. Patterns of physical activity across the lifetime

The level of participation of physical activity would be expected to vary at different ages, partly in response to changes in physical health, but also due to changes in interests, family commitments, etc. The degree to which people who are active in one age range remain active in an older age range might affect cancer risk. We explored this effect in two ways. First, we examined the degree to which physical activity in one age range was correlated with activity in a later age range. Second, we identified subjects who were consistently in the highest or lowest category of physical activity for each age range and examined their risk of CRC compared to people whose physical activity categorization fluctuated at different ages. This was performed as a sensitivity analysis. No table was included for this, as it was not part of the primary analysis.

Table 21. Association between CRC and recreational physical activities reported across the adult lifetime and colon cancer (n=865)

	Cases (n=309)		Controls (n=556)		Age and sex- adjusted OR	Fully-adjusted OR†
	No.	(%)	No.	(%)	(95% CI)	(95% CI)
Physical activity (MET-hours/week) ¹						
0	52	16.8	67	12.0	Ref.	Ref.
0 to 6.8	65	21.0	142	25.5	0.59 (0.37-0.96)	0.64 (0.39-1.05)
>6.8 to 15.0	64	20.7	121	21.8	0.71 (0.44-1.15)	0.78 (0.47-1.26)
>15.0 to 28.8	64	20.7	102	18.3	0.85 (0.52-1.37)	0.93 (0.56-1.53)
>28.8	64	20.7	124	22.3	0.72 (0.45-1.17)	0.84 (0.51-1.38)
Covariates						
BMI (<2 years prior to reference date)						
<25.0	91	29.4	165	29.7	Ref.	Ref.
25.0 to 30.0	126	40.8	260	46.8	0.84 (0.59-1.18)	0.80 (0.56-1.15)
>30.0	92	29.8	131	23.6	1.40 (0.96-2.05)	1.21 (0.80-1.80)
Smoking Status						
Never	89	28.8	211	37.9	Ref.	Ref.
Former	166	53.7	264	47.5	1.51 (1.08-2.10)	1.63 (1.14-2.32)
Current	54	17.5	81	14.6	1.77 (1.14-2.74)	1.80 (1.14-2.84)
Drinking alcohol (lifetime)						
Never	115	37.2	189	33.9	Ref.	Ref.
Ever	194	62.8	367	66.1	1.03 (0.74-1.44)	0.95 (0.66-1.35)
Regular folic acid/folate use						
No	291	94.2	519	93.3	Ref.	Ref.
Yes	18	5.8	37	6.6	0.93 (0.51-1.67)	1.03 (0.56-1.91)
Regular aspirin use						
No	227	73.5	376	67.6	Ref.	Ref.
Yes	82	26.5	180	32.4	0.68 (0.49-0.93)	0.61 (0.44-0.85)
Regular calcium use						
No	261	84.5	439	78.9	Ref.	Ref.
Yes	48	15.5	117	21.0	0.56 (0.38-0.84)	0.63 (0.42-0.96)
Diabetes						
No	242	78.3	484	87.0	Ref.	Ref.
Yes	67	21.7	72	12.9	1.61 (1.10-2.34)	1.64 (1.10-2.43)
Inflammatory Bowel Disease (IBD)						
No	304	98.4	543	97.7	Ref.	Ref.
Yes	5	1.6	13	2.3	0.69 (0.24-1.96)	0.79 (0.27-2.31)

†Multivariate logistic regression, adjusted for age, sex, BMI (weight 2 yrs prior to questionnaire), alcohol (ever 1xweek for ≥ 6 months/never), regular aspirin, calcium and folate use (at least twice a week for 1 month) (yes/no), IBD (yes/no), and smoking (never/current/former); significant values in bold

¹ Based on the univariate distribution of MET-hours among cases

*Sample size was the same for both analyses

Pearson correlation coefficients were computed for the average MET-hours per week estimated for each of the three age periods. As expected, and in accordance with much of the literature, there exists a moderate positive correlation between physical activity among the three age periods. The level of physically activity (MET-hours/week) during their 20s is moderately correlated with the level of physically activity in the 30-40s (Pearson correlation coefficient, $r=0.54, p <0.0001$) and with the level of physically activity in late adulthood ($r=0.50, p <0.0001$). The correlation between early adulthood (during their 20s) and late adulthood (since turning 50) also demonstrates moderate correlation, with $r=0.51, p <0.0001$.

There were 1287 participants who had sufficient physical activity information to construct a measure of lifetime physical activity consistency. The classification was based on whether subjects were consistently within the upper two quintiles levels or consistently report 'no physical activity'. Two hundred and twenty- five (225) participants (17.5%) were consistently within the two highest MET-hours/week quartiles for every age period and were classified as 'always high'. In contrast, 209 (16.2 %) participants reported never participating in moderate or vigorous recreational physical activities throughout their lifetime. And were classified as 'always none'. A large group ($n=411$), making up 32% of the sample, were either consistently within the lower two MET-hours/week quartiles or had reported '0' MET-hours/week for one or two age periods. They were classified as the 'low or non' group. The remaining subjects had a more varied lifetime pattern of physical activity and were classified as 'varying'.

The logistic regression models were restricted to 1088 participants, due to exclusion of subjects with missing values for covariates in model ($n=199$). Overall, there was no significant association between being consistently in the upper MET-hours/week quartile throughout the

lifetime and CRC risk compared to no activity throughout the lifetime (OR=1.16, 95% CI: 0.76-1.85). For individuals who were always categorized in the lower quartiles or had no activity for only 1 or 2 age periods, there was a non-significant reduced risk of CRC (OR=0.76, 95% CI: 0.50-1.13). Similar non-significant CRC risk reductions were observed for individuals who were in the upper quartiles for one or two age periods. Type 3 analysis of effects resulted in a p-value of >0.05.

CHAPTER 5: POPULATION-BASED CASE-CONTROL STUDY DISCUSSION

1. Overview of main results

In the present study of data from Newfoundland and Labrador, the associations between CRC and recreational physical activity were assessed separately for age periods 20-29, 30-49, and 50+ and cumulatively across the lifetime. For both cases and controls, the mean values for physical activity decreased with age. No association between the risk of CRC and physical activity was apparent when comparing highest to lowest activity levels either across the lifetime (OR: 0.99, 95% CI 0.64-1.55) or in any specific age period. When analysis was restricted to colon cancer, there was evidence suggestive of an inverse association with lifetime physical activity (OR comparing highest to lowest level: 0.84, 95% CI 0.51-1.38), but the results were non-significant. In analyses stratified by sex, there was evidence suggestive of an association between lifetime physical activity and CRC in women (OR comparing highest to lowest level: 0.58, 95% CI: 0.22-1.51) but not in men (OR comparing highest to lowest level: 1.12, 95% CI: 0.66-1.90). When patterns of physical activity were assessed, there was no significant association between being consistently in the upper MET-hours/week quartile throughout the entire adult lifetime and CRC risk compared to those who were consistently non-active throughout the lifetime (OR=1.16, 95% CI: 0.76-1.85). These results contrast with much of the existing literature.

The lack of significant associations between physical activity and CRC during each age period and across the lifetime in this study may be attributable to a variety of methodological factors including low statistical sample sizes in the highest activity groups, confounding, and misclassification. In this study, there is no evidence for a trend towards a higher protective effect

from higher levels of physical activity performed across the lifetime. This may reflect the small sample sizes in the highest activity groups. For example, only 97 cases and 90 controls were in the highest lifetime physical activity quartile (i.e., an average of 52 MET-hours per week or more across their lifetime). The relative low number of cases and controls in the highest physical activity group was consistent for each age-period. When analyses were stratified by sex, there were consistently less women in the highest activity groups than men for every age period.

Our reference group comprised participants who reported 0 MET-hours/week of moderate or vigorous physical activity during each time period or across the lifetime. This was in accordance with methods used by Boyle et al. (2011). However, the majority of previous studies used the lowest quartile as reference group, i.e., no distinction was made between people who reported zero MET-hours/week of at least moderate activity and those who reported at least some such activity. After performing a sensitivity analysis, we found no significant inverse association or trends with increasing physical activity score when using lowest quartile of MET-hours per week in place of a non-active group (data not shown). Thus, the pattern of association did not change. In fact, by using a 'lowest quartile' group as a reference group, the risk estimates may be attenuated towards the null. Due to the fact that the present study assessed moderate or vigorous intensity activities, it is possible that some participants may have had high levels of physical activity of a low intensity. In this situation, the use of '0 MET-hours/week' may have been a more appropriate reference category than the 'lowest quartile' group.

Another methodological consideration is the possibility of confounding. We were able to control for most potential known confounders in the association between physical activity and CRC. There were a few factors that were not obtained for the purpose of this study that may have

acted as confounders. These included red meat and processed meat consumption, and calcium (from dietary sources).

Alternatively, the lack of an association between physical activity and CRC in this study may point to issues related to genetic susceptibility or low physical activity levels across the population. These issues in addition to the level of physical activity performed in each age period and across the lifetime in comparison to national cancer prevention guidelines, challenges to the physical activity data collection, types of recreational physical activities reported and the population from which these participants were selected will be discussed. This chapter will address these issues and compare our methods and results from other studies that have assessed physical activity and CRC across the lifetime.

2. Consideration of results in context of the literature

Only 5 other case-control studies have assessed lifetime physical activity and CRC to date. Few studies specifically examined recreational physical activity and CRC during early adulthood. Among those who did, recreational physical activity in early adulthood had no significant effect on the risk of colon cancer (OR among women 14-22 years: 1.02, 95% CI: 0.82-1.27) (Marcus et al., 1994); (OR total physical activity at age 20: 0.52 (95% CI: 0.24-1.13) (Steindorf et al., 2005), or its subsites (OR for proximal colon cancer: 0.92, 95% CI: 0.53-1.57) (Boyle et al., 2011), but one study found a significant inverse association between distal colon cancer and physical activity during this age period (Boyle et al., 2011). Our findings are consistent with Marcus et al. (1994) who reported recreational physical activity in early adulthood were not significantly associated with the risk of CRC.

The study by Parent et al., (2010) was the only other Canadian study to assess lifetime physical activity and CRC. Their lifetime recreational physical activity analyses were confined to 201 men with colon cancer and 102 men with rectal cancer. They were the only other study that assessed lifetime physical activity and CRC that failed to demonstrate an inverse association.

Seasonality of recreational activity may explain at least in part, the lack of an association between lifetime recreational physical activity and CRC from our study and the other Canadian study by (Parent et al., 2010). For example, it is possible that seasonality inactivity throughout the lifetime could partially explain the lack of an association. Regardless of age, adverse weather may impact the amount of physical activity an individual engages in on a particular day. Numerous studies cited by Tucker and Gilliland demonstrate that adults are more active on warmer days and on days when it is not raining or snowing (Bélanger, Gray-Donald, O'Loughlin, Paradis, & Hanley, 2009). Canadian studies that compared daily weather conditions obtained from Environment Canada and a 7 day activity recall found days with snowfall or 'harsh climates' had lower physical activity (Bélanger et al., 2009). In our study of Newfoundland and Labrador residents, weather during the winter months is a factor that may have contributed to our lower activity estimates.

The study by Parent et al., 2011 also had a high proportion of cases and controls who reported low or no activity throughout their lifetime: 58.5% cases and 51.9% controls. Based on their definitions, these individuals did not engage in sports and/or outdoor activities once a week or more for at least 6 months in their lifetime. Our study collective more comprehensive physical activity data, but still had 16.4% of cases and 12.0% of controls report never engaging in any moderate or vigorous physical activity. The Canadian Community Health Survey reports have found residents of the Atlantic Provinces, Quebec, Nunavut, Manitoba and Saskatchewan

consistently below the national physical activity levels (Bélanger et al., 2009). Since a large proportion of Newfoundland and Labrador residents live in rural communities, barriers/access to physical activity may be another important factor to consider in understanding why this study and many others have found significantly lower physical activity levels in Newfoundland and Labrador in compared to the national average.

The WCRF/AICR CUP (2011) concluded that there was a stronger inverse association between CRC and recreational physical activity in men than women (World Cancer Research Fund/American Institute for Cancer Research, 2011). Once again, our results contrast with much of the literature. In our study, there was evidence of a non-significant inverse association between CRC and physical activity for every age period (excluding their 30-40s) and across the lifetime among women. For men, there was a non-significant elevation in the risk estimates when comparing highest physical activity group to those non-active for every age period and across the lifetime. Boyle et al., 2011 also found a non-significant inverse association between CRC and recreational physical for every comparable age period (including their 30-40s) and across the lifetime among women. Parent et al., 2011 also found a non-significant increase in colon cancer risk when comparing men who engaged in recreational activities often compared to those who report no activity or not often throughout their lifetime.

The differences in risk estimates when comparing highest physical activity category to non-active participants for men and women may be partially explained by different biological mechanisms through which physical activity may protect against CRC. Alternatively, the distribution and patterns of activity may differ between men and women. Data from the Canadian Community Health Survey (CCHS) suggests more men than women participate in some form of recreational physical activity (Bélanger et al., 2009). In the CCHS, a higher

percentage of men (54.8%) than women (49.7%) reported being at least moderately active in their leisure time, particularly at younger (less than 34) and older (65 or older) ages (Bélangier et al., 2009).

There is consistent and convincing evidence of an inverse association between colon cancer and physical activity. In our study, we found a non-significant association between colon cancer and lifetime recreational physical activity (OR: 0.84, 95% CI: 0.51-1.38). This suggests the inclusion of rectal cancer may attenuate the risk estimates for CRC overall towards the null. In aggregate, the evidence on the association between physical activity and rectal cancer has been interpreted as reflecting either no association (World Cancer Research Fund / American Institute for Cancer Research, 2007),(Harriss et al., 2007),(Spence et al., 2009), (C. M. Friedenreich et al., 2010; Samad, Taylor, Marshall, & Chapman, 2005) or inconclusive (International Agency for Research on Cancer, 2002) (World Cancer Research Fund/American Institute for Cancer Research, 2011). While the differences observed in colon and rectal cancer study results may be due to differences in their etiology, the possibility cannot be excluded that these differences may be explained by fewer studies examining rectal cancer in isolation and by low statistical power in compared to studies examining colon cancer (Slattery et al., 2003).

2.1. Confounding

All of our analyses were adjusted for major potential confounders, such as BMI, drinking, and smoking. In our study, obesity and overweight were consistently associated with CRC, though increases in effect estimates were greatest in early adulthood. In early adulthood, being obese was associated with a significant 3-fold increased CRC risk. Boyle et al., 2010 did not adjust for BMI, but did adjust for energy intake from food. Their results consistently found a significant inverse association between distal colon cancer and physical activity for each age

period and across the lifetime. There is some suggestion that the association between CRC and BMI is less consistent in women. Campbell et al., (2007) used the Newfoundland Registry data and found no association between CRC and BMI among women. They concluded this could be explained partially by the protective effects of estrogen derived from adipose tissue counteracting the increased risk associated with obesity (Campbell et al., 2007).

IARC concluded there is sufficient evidence in humans that both alcoholic beverages and tobacco smoking are carcinogenic agents, with *sufficient evidence* in humans (International Agency for Research on Cancer, 2012). Newfoundland has a relatively high prevalence of tobacco use in the province, with an average rate of 34% during the period of 1985-2003 (Health Canada, 2003). In a previous study by Zhao et al., which used the NFCCR and the Ontario cancer registries, there was a 96% increased risk of developing CRC among current smokers compared to a 36% increased risk among former smokers (Zhao et al., 2010). All of the studies that assessed CRC across the lifetime and different age periods controlled for smoking. Our study consistently found a significant association with smoking for each age period and across the lifetime. We categorized smoking as never, current and former smokers, as did majority of the available studies that assessed lifetime physical activity. Other authors have used pack-years (quintiles) (Parent et al., 2010; Steindorf et al., 2005).

3. Distribution of recreational physical activities

3.1. Common modes of recreational activities

The most common mode of exercise for each life period reported by participants was walking (~60%). This mode of physical activity has, however, among the lowest of the MET-values assigned (i.e., 3.5 METs) for moderate physical activities. Hunting was considered the second most common reported recreational physical activity at every age period. The activity of

hunting generally involves a lot of walking, which many perform prior to the season in order to scope the area(s) for appropriate prospective hunting locations. The Compendium of physical activities lists a variety of MET values associated with hunting, and lists ‘dragging large game carcasses’ such as moose as eliciting the highest MET values. However, the majority of participants did not specify the type of animal they were hunting, nor did they specify how many successful hunting expeditions they had. The Department of Environment and Conservation lists the typical moose hunting season to run from early September to end of December, however some areas run for 5 months (NL Environment and Conservation, 2014). Despite laws with strict restriction of hunting moose beyond the entitled average 16 weeks in Newfoundland, some individuals in this study reported hunting moose for over 6 months. As a result of these issues, it is likely the MET-hours per week associated with hunting were over-estimated. No literature to that has considered the type of activity or level of activity per activity on the overall CRC risk. As stated previously, different activities use different energy systems (i.e., aerobic and anaerobic) and therefore may have differ in their overall cancer-protective effects.

Walking is considered a moderate intensity activity, with an associated 3.5 MET value. Likewise, hunting (general form) is also considered a moderate activity. The most common activities performed may be more moderate in nature, with less engaging with vigorous activities. In our study, we combined moderate and vigorous physical activity. However, two studies that have assessed lifetime physical activity found highest risk reductions for people who engaged in high levels of vigorous activity and not moderate recreational physical activity (Slattery et al., 1997; Steindorf et al., 2005). In fact, the study by Slattery et al. (1997) (Slattery et al., 1997) found an attenuation of the risk estimates towards the null with combining moderate and vigorous recreational physical activities. There is evidence in the literature to suggest

vigorous rather than moderate intensities that protect against cancer (Wolin et al., 2009). This is an important factor that may at least partially explain the results of our study.

3.2. Proportion of active participants meeting the national physical activity guidelines

3.2.1. *General health and wellness physical activity guidelines*

Based on our results, about 50% of participants met the current guidelines from the Canadian Society for Exercise Physiology (CSEP) that state that adults (18 years and older) should aim to get at least 150 minutes (2.5 hours) of moderate- to vigorous-intensity physical activity per week (i.e., 8.75 MET-hours/week), in bouts of 10 min or more for general health and wellness (Canadian Society for Exercise Physiology, 2012).

The mean lifetime MET-hours per week score was 20.9 and the median MET-hours per week was 10.9 among all participants. A total of 209 (16.8%) of subjects did not participate in moderate or vigorous physical activities at any age period since age 20. Among active participants (>0 MET-hours per week), cases reported higher mean MET-hours per week scores: 27.7 and 22.8 for cases and controls, respectively. However, more cases (20.1%) than controls (13.7%) did not engage in any physical activities since age 20. The Canadian Community Health Survey reports have found residents of the Atlantic Provinces, Quebec, Manitoba, and Saskatchewan consistently below the national physical activity levels (Gilmour, 2007). Given only half of the participants in this study met the national health and wellness guidelines, more research is needed to investigate physical activity patterns and distributions within areas of low participation.

3.2.2. *Cancer prevention physical activity guidelines*

Other organizations have produced cancer prevention specific guidelines with recommendations ranging from 3.75 to 7 hours per week of moderate intensity physical activity.

For example, The American Cancer Society (ACS) recommends at least 45 minutes of moderate and preferably vigorous physical activity at least 5 days per week to reduce overall cancer risk (Aparicio-Ting, Friedenreich, Kopciuk, Plotnikoff, & Bryant, 2012). This translates into 11.25 to 22.50 MET-hours per week for moderate activities (activities 3-6 METs) or >22.5 MET-hours per week for vigorous activities (activities >6 METs). The USDHHS recommends that adults engage in 60 minutes of moderate to vigorous activity on most days of the week to help manage body weight and prevent weight gain, and 60 to 90 minutes of daily moderate to vigorous activity for sustained weight loss to reduce the risk of chronic disease, including cancer (Aparicio-Ting et al., 2012).

Arguably the most comprehensive review of the current evidence linking physical activity to cancer risk was completed by the WCRF/AICR (2007). They recommend that adults aim to participate in a minimum of 60 minutes of moderate activity or 30 minutes or more of vigorous activity daily as a means of reducing cancer risk (World Cancer Research Fund / American Institute for Cancer Research, 2007).

Based on the WCRF guidelines, participants would have to engage in 24.5 MET-hours per week of moderate or 21 MET-hours per week of vigorous intensity activities. Most participants in this study would not meet the WCFR cancer prevention guidelines. Only 378 (30%) of all participants in the current study meet the WCRF cancer prevention guidelines of engaging in 21 or more MET-hours per week of moderate to vigorous physical activities. Since most cases and controls did not meet these guidelines, it is possible the level of activity was not sufficient enough to provide any protective effects against CRC and may partially explain the lack of a significant risk reduction for CRC among those who exercise regularly.

For those who do not have as much time to exercise, participating in vigorous activities will require less time to obtain the same risk reductions. Future guidelines should aim to be standardized to provide recommendations for general health and well-being and for cancer prevention.

4. Familial CRC

As stated previously, Newfoundland and Labrador has a high proportion of familial forms of CRC (Green et al., 2007). FAP and HNPCC are the two major forms of inherited CRC, accounting for 3% of all CRC (Woods et al., 2005). HNPCC is the more common of the two familial forms of CRC diagnosed, and is characterized by a young age of onset of often right-sided colon cancer and may develop tumors in other sites (Woods et al., 2005). In one Newfoundland study, they found that 31% of people diagnosed with CRC had at least one first-degree relative with CRC (Green et al., 2007). Furthermore, a total of 4.6% of those subjects met the FAP or HNPCC criteria and were deemed at high risk, while another 62% of all cases had two first-or second-degree relatives with an HNPCC-related cancer (Green et al., 2007). Another Newfoundland-based study found the majority of families had a strong familial predisposition for HNPCC-related cancers but that novel genetic causes of hereditary CRC may be responsible for the high proportion of CRC in this population (Woods et al., 2005).

In our study only 6 individuals reported being diagnosed with FAP, which is a familial form of CRC. HNPCC is thought to be more common than FAP and is thought to be under-diagnosed since there is no pathogenetic marker (Green et al., 2007). However, no information was collected on HNPCC status. In addition, there is no evidence that people with HNPCC exercise less or more compared to the general population. It is possible that individuals with

HNPCC do not acquire the same benefits of physical activity compared to the general population, since the genetic process of HNPCC proceeds independently.

Undetected CRC (not specifically familial form) within the control group may better explain the possibility of an attenuation of the risk estimates. A total of 19% of controls reported having a first degree-relative with CRC, and another 20% of controls reported having a second-degree relative with CRC. This may reflect shared environmental risks and lifestyle associated with CRC, and may not necessarily reflect a genetic predisposition.

It is suggested that familial forms of CRC first form in different segments of the bowel (e.g., FAP first arising from the distal colon and rectum, and HNPCC first arising in the proximal colon) (Iacopetta, 2002). Within subjects with colon cancer (excluding those with rectal cancer), our study found more cases to have proximal (55 %) than distal colon cancer (39%). It is possible that participants in our study had HNPCC or have not yet been diagnosed but have the inherited syndrome. Due to the high incidence of familial forms of CRC in this province, it is possible that a proportion of the controls have CRC, but are asymptomatic or earlier disease states.

It has been suggested that awareness of a positive family history may influence behavior, including physical activity. In this study, cases reported higher average MET-hours per week compared to controls. In a cluster randomized trial, Ruffin et al. (2011) reported that personalized famial risk assessment (including CRC) and prevention messages modestly increased self-reported physical activity (OR = 1.47; 95% CI, 1.08-1.98) to 30 minutes or more at least five times a week from lower lengths of session and/or numbers of sessions per week.

Although it is unknown if the role of genetic predisposition outweighs the protective effects of physical activity, there is accumulating evidence that NSAIDs reduce the risk of colorectal and other cancers associated with the Lynch syndrome (Ait Ouakrim et al., 2015). Several RCTs of people with FAP found evidence that use of NSAIDs reduces the size and the number of colorectal polyps (Ait Ouakrim et al., 2015). Similarly, chemoprevention using aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to reduce the risk of CRC in the general population (Sutcliffe et al., 2013; Chubak et al., 2015). Based on this evidence, it is likely the correct ‘dose’ of physical activity may be protective in highly susceptible populations through its anti-inflammatory mechanisms.

5. Strengths and Limitations

5.1. Strengths

The PHQ took into account type, intensity, duration and frequency of recreational activities. It used both closed and open-formats, thus permitting participants to report on a variety of recreational activities, including types of recreational activities that may be more cultural or seasonal (e.g. hockey, hunting, and fishing) which were relevant for our study population. The detailed physical activities reported from the PHQ allowed us to obtain numerical MET-hours per week estimates. The majority of studies that examine recreational physical activity estimate MET-hours per week by multiplying the MET level by the number of hours per week that the activity was performed and then summing across all activities to estimate overall MET hours per week (MET-hours/wk) of leisure time physical activity energy expenditure. This method of calculating total MET-hours per week does not consider the total duration of time spent in the activity, a factor that we were able to incorporate into our analysis.

In this study, participants provided information on months per year and number of years spent participating in each activity. If we exclude this information and multiply hours per week and MET values, we are assuming they are active every month and every year in that given timeframe. Due to seasonality of some sports and recreational activities, assuming all activities are performed throughout the year every year would greatly over-estimate the risk estimates. We improved upon earlier methods by factoring in the total years spent in each activity, thus reflecting the differences in physical activity modes and personal fluctuations in activity over time. As per the recommendations made by Trembley et al., future studies should employ standardized methods for measuring and assessing levels of physical activity and its relationship to various health outcomes including CRC (Tremblay, Kho, Tricco, & Duggan, 2010).

The categorization of PA into groups for the logistic regression analysis used different cut-points for each age-period. In each case, the MET-hours per week total was categorized into quartiles based on the univariate distribution of cases. Since PA generally decreased for older age periods, we were able to retain balanced sample size in the categories by varying the cut-points. However, as a result of using different cut-offs for physical activity quartiles, we were unable to examine the impact of a constant absolute PA level across the age periods.

5.1.1. Patterns of physical activity throughout the lifetime

Few studies have examined physical activity over more than one age period. In addition to assessing the risk associated with average lifetime physical activity levels, we investigated the effect of maintaining consistently high levels of PA over the adult lifetime. To date, only 2 studies have examined this effect throughout the lifetime on CRC (Boyle et al., 2011; Steindorf et al., 2005). We also were able to identify patterns of reported recreational physical activities by age period. For example, walking was the most common mode of recreational activity in

every age period. This detail of information is not typically obtained in case-control studies, but is important and may direct future research and public health initiatives. More studies are needed that examine physical activity across the lifetime, to determine if there are differential effects during the time course of CRC.

5.2. Limitations

The current study's main limitations were the lack of data collected on occupational physical activity, sedentary behaviors, dietary habits, and family history data.

5.2.1. *Occupational physical activity*

Lifetime occupations in this study were self-reported but were excluded from the analyses due to limited data available to quantify the degree of physical activity in the reported jobs. The occupational data did not report on primary tasks, number of years, months per year, or average hours per week worked. It provided information only on the most recent job, precluding a historical reconstruction of occupationally related physical activity. The lack of an association with recreational PA in our study may reflect the fact many Newfoundland and Labrador residents obtain substantial physical activity from occupations.

In many developed countries, occupational physical activity is tending to decrease, with recreational activity becoming a primary source of energy expenditure. However, a large proportion of employed Newfoundland and Labrador residents regularly engage in physical activity as part of their occupation. In the years leading up to the collapse of the Atlantic fishery in the 1990s, 5-6 % of the labour force was employed by the fishing, hunting and trapping industries (Department of Human Resources, Labour and Employment, 2011). A large proportion of employment came from the fishing industry. Between 1999 and 2003, there were 6.8 to 8.2 thousand Newfoundland and Labrador residents employed in occupations related to

commercial fishing or the taking of finfish, shellfish, and other species, which comprises approximately 4% of employment from all industries (Gilmour, 2007). The 2006 Census found construction and related jobs to comprise the greater proportion of employment for men (Gilmour, 2007). People working in these occupations will undertake substantial levels of physical activity.

However, measuring occupational physical activities in Newfoundland may present unique challenges as many Newfoundland residents perform seasonal work, change positions or jobs, or have more than one occupation in a given timeframe. For example, it is estimated that about 1 in ten employees in Newfoundland are seasonal workers (Department of Human Resources, Labour and Employment, 2011; Statistics Canada, 2011). In addition, the rates of unemployment in Newfoundland continue to be among the highest in Canada. This may increase the proportion of individuals who obtain their physical activity through recreational means. Newfoundland and Labrador unemployment rates for the period of 1999-2003 ranged from 15.8% to 16.7% compared to the national average ranging from 6.8% to 7.7% (Department of Human Resources, Labour and Employment, 2011). As a result, there continues to be an increasing trend of employment-related geographical mobility which includes absences from places of permanent residence for the purpose of employment. We recognize however, that excluding other sources of physical activity such as occupation is a major limitation of the study and a source of measurement error.

5.2.2. *Sedentary behavior*

Recreational physical activity represents only a small fraction of total daily movement, and more attention is being directed toward the roles of sedentary behavior and incidental movement (Colley, Garriguet, et al. 2015). Sedentary behavior is defined as any activity of low (

≤1.5 metabolic equivalents) energy expenditure. It is characterized by prolonged sitting or lying down and the absence of bodily movements (Colley et al., 2011). Time spent in sedentary recreations is now recognized as not simply the absence of physical activity, but rather, a distinct risk factor for many chronic diseases and unique health effects independent of those associated with a lack of LTPA (Colley et al., 2011). The estimated relative risk (RR) and population attributable risk (PAR%) for physical inactivity and colon cancer in Canada is 1.30 and 13.8%, respectively (Warburton et al., 2010).

Our study found a total of 209 (16.8%) of all participants did not participate in any moderate or vigorous physical activity at any age period throughout their adult lifetime. Furthermore, it is unknown how many hours per week were spent in sedentary positions among individuals who were regularly active. Future studies investigating the role of physical activity and CRC should include sedentary markers including time spent sitting and in front of the television or computer. The question remains whether or not the benefits of physical activity outweighs the potential harms of sedentary behaviors.

A 2010 systematic review assessing the risk of sedentary behavior on cancer risk found a significant increased risk of colon cancer (Lynch, 2010). This review supported the potential role of adiposity and metabolic dysfunction as mechanisms in the CRC pathway. Due to the increasing evidence that sedentary behavior is potential independent risk factor for CRC, we would expect greater effects of physical activity on CRC risk in our study. Thus, failure to include this factor in our models may lead to potential confounding. In any event, more research is needed to determine how this factor affects the association between CRC risk and physical activity.

5.2.3. *Cancer stage*

Our study did not collect data on cancer stage or grade, so we could not evaluate whether the role of recreational physical activity differs according to disease stage. Errors in measurement of pre-disease exposures (e.g., 2 years prior to questionnaire) can occur if the disease has resulted in change in behavior or if cases with advanced disease recall differentially due to poor health (Slattery, Edwards, & Samowitz, 1998).

5.2.4. *Missing confounders*

We were unable to include information related to diet in this study. Dietary factors have long been associated with CRC. However, it has been difficult to identify the specific components and patterns of diet that influence CRC risk. Although the NFCCR collected data on a variety of dietary factors, including cultural aspects of diet, this data was not accessible for our analyses. As a result, we had no information on energy intake, which might theoretically be implicated in the association between physical activity and CRC. Due to cultural influences and its distinct geographic location, Newfoundland and Labrador is known for its traditional diet, including the consumption of pickled red meat (Squires et al., 2010). Pickled red meat consumption was associated with a significant increased risk of CRC in one study of Newfoundland residents (men, OR=2.07, 95% CI: 1.37-3.15; women, OR+2.51, 95% CI: 1.45-4.32) after adjusted for potential confounders (Squires et al., 2010). In addition, data on red meat and processed meat have shown consistently higher risks for CRC in the literature (World Cancer Research Fund / American Institute for Cancer Research, 2007). IARC recently concluded that consumption of red meat is ‘probably carcinogenic to humans’, based on ‘limited evidence’ (Group 2A), and that processed meat is carcinogenic to humans based on ‘sufficient evidence’ (Group 1) (Bouvard et al., 2015).

The study did not provide a measure of abdominal obesity (e.g. waist circumference). Body fatness or adiposity is associated with CRC. In this study, BMI was used as a measure of body fatness, or adiposity. While BMI is considered a good measure of body fat percentage, it does not distinguish between adipose tissue and non-adipose tissue including lean mass. For example, athletes with a low body fat and high muscle mass tend to have a high BMI. A measure of abdominal obesity would complement BMI in the examination of the impact of obesity in CRC risk. In the majority of the literature, strong associations between BMI and CRC risk have been reported in men only. However, abdominal obesity (as determined by waist circumference) is reported to be strongly associated with CRC cancer both in men and in women (WCRF, 2007).

5.2.5. Selection Bias

Selection bias is present when individuals have different probabilities of being included in the study with respect to relevant exposures and outcomes of interest, resulting in non-comparable groups being studied (Wacholder, McLaughlin, Silverman, & Mandel, 1992). It is suggested that controls be selected from the same source population that gave rise to the study case within a specified timeframe (Wacholder et al., 1992). In our study, the source population includes all residents of Newfoundland. Cases include all residents *diagnosed* in the province between 1999 and 2003, whereas controls were recruited using Random Digit Dialing (RDD) methods, requiring them to live in the province at the time of recruitment. Cases could have left the province by the time of recruitment. This raises a potential for selection bias. Selection bias might also arise since cases whose disease is further progressed are less likely to participate in the study (Slattery et al., 1998).

RDD recruitment of controls raises a third potential for selection bias. RDD continues to face challenges including increases in unlisted telephone numbers, large and increasing proportions of cell-phone only households, incomplete telephone coverage, call screening and blocking methods, and increased non-response due to refusals.

5.2.6. *Recall Bias*

Due to the case-control study design, data is collected retrospectively which increases the risk of recall bias. This may bias the estimate of the exposure-disease association in either direction (toward or away from the null). Empirical evidence has found no relationship between the absolute differences in agreement between cases and controls and the overall level of agreement, in contradiction to suggestions in previous literature (Chouinard & Walter, 1995). Thus, it is unlikely recall bias influenced our results greatly. In this study that included both closed-ended and open-ended physical activity questions, it is possible that recall bias may exist (particularly with less commonly performed activities and those performed during their 20s). However, the effect of recall bias is unlikely to account for the lack of significant associations between CRC and physical activity. The bias is non-differential, thus it would affect both cases and controls similarly.

5.2.7. *Measurement Error*

The categorization of physical activities into group may introduce measurement error. The eight categories of activities listed in the questionnaire were somewhat arbitrary. For example, “calisthenics, aerobics, vigorous dance (including ballet), using a rowing machine, and lifting weights” were combined as one of the 8 physical activities or groups of activities listed in the closed-ended format. These activities use different energy systems (i.e., aerobic and anaerobic) and therefore may have differences in their overall cancer-protective effects. As

another example, the PHQ listed football, soccer, rugby, and basketball as one item. However, soccer is largely aerobic, whereas football utilizes various energy sources but is largely anaerobic. Anaerobic metabolism does not metabolize glucose as efficiently which might impact on the potential protective benefits of physical activity.

The open-ended section of the PHQ permitted participants to list additional strenuous activities. Coding and interpreting the responses to the open-ended questions was complicated by issues such as ambiguity, spelling errors, and the use of slang, which increase the risk of measurement error.

The PHQ was based on activities of moderate or vigorous intensities. Some participants reported light activities among the open-ended questions. For example, cutting hay is often performed using a harvester, or tractor, and has an assigned MET value of 2.5 according to the Compendium of Physical Activities (Ainsworth et al., 2011). Activities with a MET value under 3 were considered to be sedentary or light activities and were excluded from the analyses as all participants were asked to report only strenuous activities. However, it is possible that the accumulation of light, moderate, and vigorous activities throughout the day (that is, total-MET-hours) rather than average MET-hours are protective. In that case, exclusion of light activities would introduce measurement error into the MET-hour/week estimates. Likewise, it is possible it is the total activity from all activity types (including recreational, occupational, and transport) that protects against CRC, or is more protective than moderate-to-vigorous recreational intensities alone. The exclusion of occupational activities would lead to a bias in the estimation of PA categories.

Some measurement errors may be similar among cases and controls and may lead to non-differential recall bias. For example, consider the questions asking participants to recall

strenuous activity. The examples provided in the questionnaire (e.g. hunting and sledding), may be misleading, particularly in a province where ‘sledding’ is often a term used to describe ‘snow-mobiling’, and the energy expended while hunting is dependent upon the type of animal, and whether or not an animal was caught. Errors of this type would occur with both case and controls. Non-differential errors tend to attenuate the estimate of the association towards the null.

6. Conclusion

Overall, this study that used data from the Newfoundland Colorectal Cancer Registry found no association between high levels of physical activity throughout the lifetime and CRC risk compared to people who engage in no moderate or vigorous physical activity throughout their lifetime. Likewise, we no found significant effects or trends in the association between physical activities performed during any specific age-period. The lack of a significant association in this study may in part be due to limitations with the study including the inclusion of rectal cancer within the outcome of interest, combining moderate and vigorous-intensity activities, and the lack of occupational physical activities for this population. Future studies should incorporate total physical activity (i.e., recreational, occupational, and household) across the lifetime while investigating the effects of sedentary behavior within this relationship. Additional studies also need to consider family history and susceptibility genes to determine the effect of physical activity on a ‘high or intermediate risk’ population, such as Newfoundland. Future guidelines should also aim to use standardized definitions for physical activity, and to comment on the levels of physical activity reported in comparison to current national physical activity guidelines specifically for cancer prevention. More research is needed in the investigation between CRC and lifetime physical activity. Physical activity measurement using

movement monitors in addition to comprehensive questionnaires may help improve the quality of future studies.

References

- Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckles, N., Bassett, D. R., Tudor-Locke, C., Leon, A. S. (2011). **2011 Compendium of Physical Activities: A second update of codes and MET values.** *Med Sci Sports Exerc*, 43(8):1575-81.
- Albanes, D., Conway, J. M., Taylor, P. R., Moe, P. W., & Judd, J. (1990). **Validation and comparison of eight physical activity questionnaires.** *Epidemiology*, 1, 65-71.
- Aparicio-Ting, F. E., Friedenreich, C., Kopciuk, K. A., Plotnikoff, R. C., & Bryant, H. E. (2012). **Prevalence of meeting physical activity guidelines for cancer prevention in alberta.** *Chronic Diseases and Injuries in Canada*, 32(4), 1-12.
- Bélanger, M., Gray-Donald, K., O'Loughlin, J., Paradis, G., & Hanley, J. (2009). **Influence of weather conditions and season on physical activity in adolescents.** *Ann Epidemiol.*, 19(3), 180-186.
- Bouvard, V., Loomis, D., Guyton, K., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Mattock, H., Straif, K. (International Agency for Research on Cancer Monograph Working Group) (2015). **Carcinogenicity of consumption of red and processed meat.** *The Lancet*: 16(16): 1599-1600.
- Boyle, T., Heyworth, J., Bull, F., McKerracher, S., Platell, C., & Fritschi, L. (2011). **Timing and intensity of recreational physical activity and the risk of subsite-specific colorectal cancer.** *Cancer Causes & Control*, 22, 1647-1658.

Campbell, P., Cotterchio, M., Dicks, E., Parfrey, P., Gallinger, S., & McLaughlin, J. (2007).

Excess body weight and colorectal cancer risk in Canada: Associations in subgroups of clinically defined familial risk of cancer. *Cancer Epidemiol Biomarkers Prev*, 16, 135-1741.

Canadian Cancer Society's Advisory Committee on Cancer Statistics. (2015). **Canadian cancer statistics 2015.** Toronto, ON.

Canadian Partnership Against Cancer. (2014) **Colorectal cancer screening in Canada: Monitoring & evaluation of quality indicators – results report, January 2011 – December 2012.**

Canadian Society for Exercise Physiology. (2012). **Canadian physical activity guidelines Canadian sedentary behavior guidelines.**

Chouinard, E., & Walter, S. (1995). **Recall bias in case-control studies: An empirical analysis and theoretical framework.** *Journal of Clinical Epidemiology*, 48(2), 245-254.

Chubak J, Kamineni A, Buist DSM, Anderson ML, Whitlock EP. (2015) **Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force.** Agency for Healthcare Research and Quality. Rockville (MD): 15-05228-EF-1.

Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clarke, J., & Tremblay, M. S. (2011). **Physical activity of Canadian adults: Accelerometer results from the 2007 to 2009 Canadian health survey.** *Health Reports (Statistics Canada, Catalogue 82-003)*, 22

Csizmadi, I., Siou, G. L., Friedenreich, C. M., Owen, N., & Robson, P. J. (2011). **Hours spent and energy expended in physical activity domains: Results from the tomorrow project cohort in Alberta, Canada.** *International Journal of Behavioral Nutrition and Physical Activity*, 8(110), 1-11.

Department of Human Resources, Labour and Employment. (2011). *Newfoundland and Labrador labour market Outlook 2020*.

Diaz, K., Krupta, D.J., Chang, M., Peacock, J., Ma, Y., Goldsmith, J., Schwartz, J., Davidson, K. (2015) **Fitbit®: An accurate and reliable device for wireless physical activity tracking.** *International Journal of Cardiology*,185: 138–140

Drake, R. L., Vogl, W., & Mitchell, A. W. (2010). **Gray's anatomy for students** (2nd ed.) Churchill Livingstone/Elsevier.

Ekoé, J., Zimmet, P., & Williams, R. (2001). **The epidemiology of diabetes mellitus: An international perspective.** Chichester, UK.: John Wiley & Sons, Ltd,.

Evenson, K., Goto, M., Furberg, R. (2015); **Systematic review of the validity and reliability of consumer-wearable activity trackers.** *International Journal of Behavioral Nutrition and Physical Activity*,12:159: 1-22.

Folsam, A. R., Jacobs, D. R., Caspersen, C. J., Gomez-Marin, O., & Knudsen, J. (1986). **Test-retest reliability of the minnesota leisure time physical activity questionnaire.** *Journal of Chronic Diseases*, 39(7), 505-511.

- Friedenreich, C. M. (2001). **Physical activity and cancer prevention: From observational to intervention research** . *Cancer Epidemiology, Biomarkers & Prevention*, *10*, 287-301.
- Friedenreich, C. M., Neilson, H. K., & Lynch, B. M. (2010). **State of the epidemiological evidence on physical activity and cancer prevention**. *European Journal of Cancer*, *46*(14), 2593-2604. doi:10.1016/j.ejca.2010.07.028
- Friedenreich, C., Norat, T., Steindorf, K., Boutron-Ruault, M. C., Pischon, T., & Mazuir, M. (2006). **Physical activity and risk of colon and rectal cancers: The European prospective investigation into cancer and nutrition**. *Biomarkers Prev*, (15), 2398-2407.
- Friedenreich, C. M., Courneya, K. S., & Bryant, H. (1998). **The lifetime total physical activity questionnaire: Development and reliability**. *Med Sci Sports Exerc*, *30*(2), 266-274.
- Garber C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.M., Nieman, D.C., Swain, D.P. (2011) **American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise**. *Med Sci Sports Exerc* *43*: 1334-1359.
- Gilmour, H. (2007). **Physically active Canadians**. *Health Reports (Statistics Canada, Catalogue 82-003)*, *18*(3), 45-65.
- Giovannucci, E. (2003). **Diet, body weight, and colorectal cancer: A summary of the epidemiologic evidence**. *Journal of Women's Health*, *12*(2), 173-182.

Giovannucci, E., Ascherio, A., Rimm, E. B., Colditz, G. A., Stampfer, M. J., & Willett, W. C.

(1995). **Physical activity, obesity, and risk of colon cancer and adenoma in men.** *Ann Intern Med.*, 122, 327-334.

Godin, G. & Shephard, R.J. (1985). **A simple method to assess exercise behavior in the community.** *Can J Appl Sport Sci*, 10(3), 141-146.

Green, R. C., Green, J. S., Buehler, S. K., Robb, J. D., Daftary, D., Gallinger, S., . . .

Younghusband, H. B. (2007). **Very high incidence of familial colorectal cancer in Newfoundland: A comparison with Ontario and 13 other population-based studies.** *Familial Cancer*, 6, 53-62.

Harriss, D. J., Cable, N. T., George, K., Reilly, T., Renehan, A. G., & Haboubi, N. (2007).

Physical activity before and after diagnosis of colorectal cancer: Disease risk, clinical outcomes, response pathways and biomarkers. *Sports Med*, 37, 947-960.

Health Canada. (2003). **Smoking in Canada: An Overview.**

Helmerhorst, H., Brage, S., Warren, J., Besson, H., Ekelund, U. (2012). **A systematic review of**

reliability and objective criterion-related validity of physical activity questionnaires. *International Journal of Behavioral Nutrition and Physical Activity*, 9; 103:1-55.

Huxley, R. R., Ansary-Moghaddam, A., Clifton, P., Czernichow, S., Parr, C. L., & Woodward,

M. (2009). **The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence,** *Int J Cancer*, 125, 171-180.

Iacopetta, B. (2002). **Are there two sides to colorectal cancer?** *Int J Cancer*, 101, 403-408.

- International Agency for Research on Cancer. (2002). **Characteristics of weight control and physical activity.** In H. Vainio, & F. Bianchini (Eds.), *Weight control and physical activity. IARC handbook of cancer prevention* (pp. 1-12). Lyon, France: IARC Press.
- International Agency for Research on Cancer. (2012). *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Vol 100E. A review of human carcinogens: Personal habits and indoor combustions.* Lyon, France: IARC.
- Kaiyala, K. J. (2014). **What does indirect calorimetry really tell us?** *Mol Metab.* 2014 Jul; 3(4): 340–341., 4(4), 340-341.
- Kaiyala, K. J., & Schwartz, M. W. (2011). **Toward a more complete (and less controversial) understanding of energy expenditure and its role in obesity pathogenesis.** *Diabetes*, 60, 17-23.
- Lamb, K. L., & Brodie, D. A. (1991). **Leisure-time physical activity as an estimate of physical activity: A validation study.** *J Clin Epidemiol.*, 44, 41-52.
- Laporte, R. E., Montoye, H. J., & Caspersen, C. J. (1985). **Assessment of physical activity in epidemiologic research: Problems and prospects.** *Public Health Reports*, 100, 131-146.
- Larsson, S. C., Orsini, N., & Wolk, A. (2005). **Diabetes mellitus and risk of colorectal cancer: A meta-analysis.** *J Natl Cancer Inst.*, 97, 1679–87.
- Larsson, S. C., Rutegard, J., Bergkvist, L., & Wolk, A. (2006). **Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men.** *Eur J Cancer.*, 42, 2590-2597.

- Lee, K. J., Inoue, M., Otani, T., Iwasaki, M., Sasazuki, S., Tsugane, S., & JPHC Study Group. (2007). **Physical activity and risk of colorectal cancer in Japanese men and women: The Japan Public health Center-based prospective study.** *Cancer Causes Control, 18*(2), 199-209.
- Levi, F., Pasche, C., & Lucchini, F. (1999). **Occupational and leisure-time physical activity and the risk of colorectal cancer.** *Eur J Cancer Prev, 8*, 487-493.
- Little, J., & Sharp, L. (2008). **Epidemiology of colorectal cancer.** In J. Cassidy (Ed.), *International handbook of colorectal cancer* (pp. 1-33) Euromed.
- Lynch, B. M. (2010). **Sedentary behavior and cancer: A systematic review of the literature and proposed biological mechanisms.** *Cancer Epidemiol Biomarkers Prev, 19*(11), 2691-2709.
- Marcus, P. M., Newcomb, P. A., & Storer, B. E. (1994). **Early adulthood physical activity and colon cancer risk among Wisconsin women.** *Cancer Epidemiol Biomarkers Prev, 3*, 641-644.
- Morson, B. C. (1976). **Genesis of colorectal cancer.** *Clin Gastroenterol, 5*, 505-525.
- NL Environment and Conservation. (2014). *Hunting and trapping guide 2014-2015.*
- Ait Ouakrim, D., Dashti, S.G., Chau, R. (2015) **Aspirin, Ibuprofen, and the Risk for Colorectal Cancer in Lynch Syndrome.** *J Natl Cancer Inst, 107* (9)

- Parent, M., Rousseau, M., El-Zein, M., Latreille, B., Desy, M., & Siemiatycki, J. (2010). **Occupational and recreational physical activity during adult life and the risk of cancer among men.** *Cancer Epidemiology*, 35(2011), 151-159.
- Pham, N. M., Mizoue, T., Tanaka, K., Tsuji, I., Tamakoshi, A., Matsuo, K., Tanaka, K. (2012). **Physical activity and colorectal cancer risk: An evaluation based on a systematic review of epidemiologic evidence among the Japanese population.** *Japanese Journal of Clinical Oncology*, 42(1), 2-13.
- Quadrilatero, J., & Hoffman-Goetz, L. (2003). **Physical activity and colon cancer: A systematic review of potential mechanisms.** *Journal of Sports Medicine and Physical Fitness*, 43(2), 121-138.
- Richardson, M. T., Leon, A. S., Jacobs, D. R., Ainsworth, B. E., & Serfass, R. (1994). **Comprehensive Minnesota Leisure –Time physical activity questionnaire.** *J Clin Epidemiol.*, 47, 271-281.
- Robsahm, T. E., Aagnes, B., Hjartaker, A., Langseth, H., Bray, F., & Larsen, I. K. (2013). **Body mass index, physical activity, and colorectal cancer by anatomical subsites: A systematic review and meta-analysis of cohort studies.** *European Journal of Cancer Prevention*, 22, 492-505.
- Rubenstein, J. H., Morgenstern, H., Kellenberg, J., Kalish, T., Donovan, J., Inadomi, J., Scheonfeld, P. (2011). **Validation of a new physical activity questionnaire for a sedentary population.** *Dig Dis Sci.*, 56(9), 2678-2687.

- Ruffin, M.T., Nease, D.E. Jr., Sen, A., Pace, W.D., Wang, C., Acheson, L.S., Rubinstein, W.S., O'Neill, S., Gramling, R.; Family History Impact Trial (FHITr) Group. (2011). **Effect of preventive messages tailored to family history on health behaviors: the Family Healthware Impact Trial.** *Ann Fam Med.* **9(1): 3-11**
- Sallis, J. F. (1985). **Physical activity assessment methodology in the Stanford five-cities project.** *Am.J.Epidemiol.*, *121*, 91-106.
- Samad, A. K., Taylor, R. S., Marshall, T., & Chapman, M. A. (2005). **A meta-analysis of the association of physical activity with reduced risk of colorectal cancer.** *Colorectal Dis*, *7*, 204-213.
- Severson, R. K., Nomura, M. Y., Grove, J. S., & Stemmermann, G. N. (1989). **A prospective analysis of physical activity and cancer.** *Am J Epidemiol*, *130(3)*, 522-529.
- Shepard, R. J. (2012). **Limits to the measurement of habitual physical activity by questionnaires.** *Br.J.Sports Med*, *37(197-206)*
- Shepard, R. J. (1990). **Physical activity and cancer.** *Int.J.SportsMed*, *11*, 413-420.
- Shepard, R. J. (2003). **Limits to the measurement of habitual physical activity by questionnaires.** *Br J Sports Med*, *37*, 197-206.
- Slattery, M. L. (2004). **Physical activity and colorectal cancer.** *Sports Med*, *34(4)*, 239-252.
- Slattery, M. L., Edwards, S., Curtin, K., Ma, K., Edwards, R., Holubkov, R., & Schaffer, D. (2003). **Physical activity and colorectal cancer.** *Am J Epidemiol*, *159*, 214-224.

Slattery, M. L., Edwards, S. L., & Ma, K. (1997). **Physical activity and colon cancer: A public health perspective.** *Ann.Epidemiol.*, 7, 137-145.

Slattery, M. L., Edwards, S. L., & Samowitz, W. S. (1998). **Stage of colon cancer at diagnosis: Implications for risk factor associations?** *International Journal of Epidemiology*, 27, 382-387.

Slattery, M. L., & Jacobs, D. R. (1995). **Assessment of ability to recall activity of several years ago.** *Ann.Epidemiol.*, 5, 292-296.

Spence, R. R., Heecsh, C. C., & Brown, W. J. (2009). **A systematic review of the association between physical activity and colorectal cancer risk.** *Scand J Med Sci Sports*, 19, 764-781.

Squires, J., Roebathan, B., Buehler, S., Sun, Z., Cotterchio, M., Younghusband, H. B., Wang, P. P. (2010). **Pickled meat consumption and colorectal cancer (CRC): A case-control study in Newfoundland and Labrador, Canada.** *Cancer Causes Control*, 21, 1513-1521.

Statistics Canada. (2011). *Health trends*. (No. Catalogue No. 82-213-XWE.). Ottawa: Statistics Canada. Retrieved from <http://www12.statcan.gc.ca/health-sante/82-213/index.cfm?Lang=ENG>

Steindorf, K., Jedrychowski, W., Schmidt, M., Popiela, T., Penar, A., Galas, A., & Wahrendorf, J. (2005). **Case-control study of lifetime occupational and recreational physical activity and risks of colon and rectal cancer.** *Eur J Cancer Prev*, 14(4), 363-371.

- Sun, L., & Yu, S. (2012). **Diabetes mellitus is an independent risk factor for colorectal cancer.** *Dig Dis Sci.*, 6, 1586-97.
- Sutcliffe, P., Connock, M., Gurung, T., Freeman, K., Johnson, S., Kandala, N.B., Grove, A., Gurung, B., Morrow, S., Clarke, A. (2013) **Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews.** *Health Technol Assess.* 17(43):1-253.
- Taylor, H. L. (1978). **A questionnaire for the assessment of leisure-time physical activities.** *J Chronic Dis*, 31, 741-755.
- Thune, I., & Lund, E. (1996). **Physical activity and risk of colorectal cancer in men and women.** *Br.J.Cancer*, 73, 1134-1140.
- Tremblay, M. S., Kho, M. E., Tricco, A. C., & Duggan, M. (2010). **Process description and evaluation of Canadian physical activity guidelines development.** *International Journal of Behavioral Nutrition and Physical Activity*, 7, 42.
- Vena, J. E., Graham, S., Zielezny, M., Swanson, M. K., Barnes, R. E., & Nolan, J. (1985). **Lifetime occupational exercise and colon cancer.** *Am.J.Epidemiol.*, 122(3), 357-365.
- Wacholder, S., Silverman, D. T., McLaughlin, J. K., & Mandel, J. S. (1992). **Selection of controls in case-control studies II: Types of controls.** *Am.J.Epidemiol.*, 135(9), 1029-1041.
- Wacholder, S., McLaughlin, J. K., Silverman, D. T., & Mandel, J. S. (1992). **Selection of controls in case-control studies, I. principles.** *Am.J.Epidemiol.*, 135(9), 1019-1028.

- Warburton, D. E. R., Charlesworth, S., Ivey, A., Nettlefold, L., & Bredin, S. S. D. (2010). **A systematic review of the evidence for Canada's physical activity guidelines for adults.** *International Journal of Behavioral Nutrition and Physical Activity*, 7(39), 1-220.
- Wei, E. K., Giovannucci, E., Wu, K., Rosner, B., Fuchs, C. S., Willet, W., & Colditz, G. A. (2003). **Comparison of risk factors for colon and rectal cancer.** *Int J Cancer*, 108, 433-442.
- Wei, E. K., Wolin, K. Y., & Colditz, G. A. (2011). **Time course of risk factors in cancer etiology and progression.** *J Clin Oncology*, 28(26), 052-4057.
- Williams, K. (2011). *EPI 5345: Applied logistic regression*. University of Ottawa;:
- Wolin, K. Y., Yan, Y., Colditz, G. A., & Lee, I. M. (2009). **Physical activity and colon cancer prevention: A meta-analysis.** *Br.J.Cancer*, 100, 611-616.
- Woods, M. O., Hyde, A. J., Curtis, F. K., Stuckless, S., Green, J. S., Pollett, A. F., . . . Parfrey, P. S. (2005). **High frequency of hereditary colorectal cancer in Newfoundland likely involves novel susceptibility genes.** *Clin Cancer Res*, 11, 6853-6861.
- Woods, M. O., Younghusband, H. B., Parfrey, P. S., Gallinger, S., McLaughlin, J., Dicks, E., . . . Green, R. C. (2010). **The genetic basis of colorectal cancer in a population-based incident cohort with a high rate of familial disease.** *Gut*, 59, 1369-1377.
- World Cancer Research Fund / American Institute for Cancer Research. (2007). **Food, nutrition, physical activity, and the prevention of cancer: A global perspective.** Washington DC: AICR.

World Cancer Research Fund/American Institute for Cancer Research. (2011). **Continuous update project interim report summary: Food, nutrition, physical activity, and the prevention of colorectal cancer.** Washington DC: AICR.

Zhao, J., Halfyard, B., Roebathan, B., West, R., Buehler, S., Sun, Z., Wang, P. P. (2010). **Tobacco smoking and colorectal cancer: A population-based case-control study in Newfoundland and Labrador.** *Canadian Journal of Public Health*, 101(4), 281-289.

APPENDIX 1

NFCCR Personal Health Questionnaire (PHQ)

**Newfoundland
Familial Colon Cancer Study**

Personal History Questionnaire

This questionnaire is about factors that may relate to a person's risk of cancer. It is important to have complete information for scientific reasons and we encourage you to answer all of the questions. But if you come to a question that you don't want to answer, put an "X" beside it and go on with the rest of the questions.

Should you wish to talk to someone about this questionnaire, please call our Study
Coordinator Elizabeth Dicks
Toll Free 1-888-908-4988 or in St. John's 777-8040

Please write in your answers where space is provided, or place tick marks in circles ①

What date are you filling out this questionnaire? ___ / ___ / ___
 day month year

Identifying Information

1. Are you male or female? male
 female
2. What is your age? ___ years
 don't know
3. What is your date of birth? day
 month
 year ___ ___ ___
 don't know day
 don't know month
 don't know year
4. Are you a twin or triplet? yes, a twin
 yes, other multiple (triplet, quadruplet, etc.): _____
please specify
 no
 don't know

If yes, please read the following statement and answer the question.
 Non-identical twins are no more alike than ordinary brothers and sisters. Genetically identical twins, on the other hand, look so much alike (that is, they have a strong resemblance to each other in height, colouring, features of the face, etc.) that people often mistake one for the other, especially during their childhood.
 Do you have a genetically identical twin or triplet?
 yes
 no
 don't know
5. What is your marital status? currently married or living as married
 separated
 divorced
 widowed
 single or never married
 don't know

Bowel Screening and Health

6. Have you ever had a test for blood in your stool, called a smear test or a hemocult? This test is frequently done as part of a routine physical examination, or it can be done at home.
 yes
 no *Please go to #7*
 don't know *Please go to #7*
- 6a. When did you first have this test?
 age when first tested ___ ___
or
 year of first test ___ ___ ___
 don't know
- 6b. What were the reasons for your first test?
Please tick all that apply.
 to investigate a new problem
 family history of colorectal cancer
 routine/yearly examination or check-up
 follow-up of a previous problem
 other: _____
please specify
 don't know
- 6c. How many times have you had a hemocult test?
 ___ number of hemocult tests
 don't know
- 6d. If you have had a hemocult test more than once, when did you last have this test?
 age when last tested ___ ___
or
 year of last test ___ ___ ___
 don't know
7. Have you ever had a sigmoidoscopy? Sigmoidoscopy involves looking inside the lower bowel and rectum with a lighted instrument. This examination is usually done in a doctor's office without anesthesia.
 yes
 no *Please go to #8*
 don't know *Please go to #8*
- 7a. When did you first have this test?
 age when first tested ___ ___
or
 year of first test ___ ___ ___
 don't know
- 7b. What were the reasons for your first sigmoidoscopy? *Please tick all that apply.*
 to investigate a new problem
 family history of colorectal cancer
 routine/yearly examination or check-up
 follow-up of a previous problem
 other: _____
please specify
 don't know
- 7c. How many times have you had a sigmoidoscopy?
 ___ number of sigmoidoscopies
 don't know
- 7d. If you have had a sigmoidoscopy more than once, when did you last have this test?
 age when last tested ___ ___
or
 year of last test ___ ___ ___
 don't know

8. Have you ever had a colonoscopy?
Colonoscopy is an examination of the entire large bowel using a long flexible instrument. This examination is usually done under sedation.

- yes
 no *Please go to #9*
 don't know *Please go to #9*

8a. When did you first have this test?

age when first tested _____
or
year of first test _____
 don't know

8b. What were the reasons for your first colonoscopy? *Please tick all that apply.*

- to investigate a new problem
 family history of colorectal cancer
 routine/yearly examination or check-up
 follow-up of a previous problem
 other: _____
please specify
 don't know

8c. How many times have you had a colonoscopy?

___ number of colonoscopies
 don't know

8d. If you have had a colonoscopy more than once, when did you last have this test?

age when last tested _____
or
year of last test _____
 don't know

9. Has a doctor ever told you that you had polyps in your large bowel or colon or rectum? Polyps are growths in the lining of the colon which vary in size from a tiny dot to several inches.

- yes
 no *Please go to #10*
 don't know *Please go to #10*

9a. When did your doctor first tell you that you had polyps?

age at first diagnosis _____
or
year of first diagnosis _____
 don't know

9b. Have you been told more than once that you had polyps?

- yes
 no
 don't know

9c. When did your doctor last tell you that you had polyps?

age at last diagnosis _____
or
year of last diagnosis _____
 don't know

9d. Do you know what kind of polyps they were? *Please include all the separate times you were told you had polyps. Please tick all that apply.*

- benign
 adenomatous (pre-cancerous)
 hyperplastic
 other: _____
please specify
 don't know

9e. Did you have the polyps removed (by a procedure called a polypectomy)? (This can be done during a sigmoidoscopy or colonoscopy.)

- yes
 no *Please go to #10*
 don't know *Please go to #10*

9f. When did you first have polyps removed?

age at first polypectomy _____
or
year of first polypectomy _____
 don't know

9g. Have you had polyps removed more than once?

- yes
 no
 don't know

9h. If you have had polyps removed more than once, when did you last have polyps removed?

age at last polypectomy _____
or
year of last polypectomy _____
 don't know

10. Has a doctor ever told you that you had familial adenomatous polyposis, known also as FAP? This is a condition, sometimes occurring in families, in which numerous polyps line the inside of the large bowel or colon.

- yes
 no *Please go to #11*
 don't know *Please go to #11*

10a. When did your doctor first tell you that you had FAP?

age at diagnosis _____
or
year of diagnosis _____
 don't know

11. Has a doctor ever told you that you had Crohn's disease? This is where you have an inflammation that extends into the deeper layers of the intestinal wall. It may also affect other parts of the digestive tract, including the mouth, esophagus, stomach, and small intestine.

- yes
 no *Please go to #12*
 don't know *Please go to #12*

11a. When did your doctor first tell you that you had Crohn's disease?

age at diagnosis _____
or
year of diagnosis _____
 don't know

12. Has a doctor ever told you that you had ulcerative colitis? This is an inflammation and ulceration of the lining of the bowel (colon) and rectum. It is not a stomach ulcer.

- yes
 no *Please go to #13*
 don't know *Please go to #13*

12a. When did your doctor first tell you that you had ulcerative colitis?

age at diagnosis _____
or
year of diagnosis _____
 don't know

13. Has a doctor ever told you that you had irritable bowel syndrome? This is a disorder of the bowels leading to cramping, gassiness, bloating and alternating diarrhoea and constipation. It is sometimes called IBS, or spastic colon.

- yes
 no *Please go to #14*
 don't know *Please go to #14*

13a. When did your doctor first tell you that you had irritable bowel syndrome?

age at diagnosis _____

or

year of diagnosis _____

don't know

14. Has a doctor ever told you that you had diverticular disease? This may also be called diverticulosis or diverticulitis. It's a condition in which the bowel may become infected, and can lead to pain and chronic problems with bowel habits.

yes

no _____ Please go to #15

don't know _____ Please go to #15

14a. When did your doctor first tell you that you had diverticular disease?

age at diagnosis _____

or

year of diagnosis _____

don't know

15. Have you ever had any of your large bowel or colon removed?

yes

no _____ Please go to #16

don't know _____ Please go to #16

Was it completely removed, or was only part of it removed?

completely removed

partly removed

don't know

15a. When did you first have any of your bowel or colon removed?

age at first operation _____

or

year of first operation _____

don't know

15b. Have you had more than one surgery to remove your bowel or colon?

yes

no _____ Please go to #16

don't know _____ Please go to #16

15c. When did you last have all or part of your bowel or colon removed?

age at last operation _____

or

year of last operation _____

don't know

16. Have you had your gallbladder removed?

yes

no _____ Please go to #17

don't know _____ Please go to #17

16a. When did you have your gallbladder removed?

age at operation _____

or

year of operation _____

don't know

17. Has a doctor ever told you that you had diabetes, also known as diabetes mellitus? Please do not include diabetes which you had only during pregnancy.

yes

no _____ Please go to #18

don't know _____ Please go to #18

17a. When did your doctor first tell you that you had diabetes?

age at diagnosis _____

or

year of diagnosis _____

don't know

17b. Did you ever take medication to control your diabetes?

yes

no _____ Please go to #18

don't know _____ Please go to #18

17c. What type of medication did you use, pills or insulin injections?

pills

insulin injections

both

don't know _____ Please go to #18

17d. How often did you usually take it? Please choose the most appropriate category.

Pills Insulin

times per day or

times per week or

times per month or

times per year

don't know

17e. About two years ago, were you taking it?

Pills Insulin

yes

no

don't know

17f. How long, in total, have you taken this medication?

Pills Insulin

number of months or

number of years

don't know

18. Has a doctor ever told you that you had high cholesterol? If your doctor told you it was borderline, please tick no.

yes

no _____ Please go to #19

don't know _____ Please go to #19

18a. When did your doctor first tell you that you had high cholesterol?

age at diagnosis _____

or

year of diagnosis _____

don't know

18b. Did you ever take medication to control your high cholesterol?

yes

no _____ Please go to #19

don't know _____ Please go to #19

18c. How often did you usually take it? Please choose the most appropriate category.

_____ times per day or

_____ times per week or

_____ times per month or

_____ times per year

don't know

18d. About two years ago, were you taking it?

yes

no

don't know

18e. How long, in total, have you taken this medication?

_____ number of months or

_____ number of years

don't know

19. Has a doctor ever told you that you had high levels of fat (other than cholesterol) in your blood, also called high triglycerides? *If your doctor told you it was borderline, please tick no.*

- yes
 no *Please go to #20*
 don't know *Please go to #20*

19a. When did your doctor first tell you that you had high triglycerides?

- age at diagnosis _____
or
year of diagnosis _____
 don't know

19b. Did you ever take medication to control the high levels of fat in your blood?

- yes
 no *Please go to #20*
 don't know *Please go to #20*

19c. How often did you usually take it? *Please choose the most appropriate category.*

- _____ times per day *or*
_____ times per week *or*
_____ times per month *or*
_____ times per year
 don't know

19d. About two years ago, were you taking it?

- yes
 no
 don't know

19e. How long, in total, have you taken this medication?

- _____ number of months *or*
_____ number of years
 don't know

20. Has a doctor ever told you that you had any type of cancer?

- yes
 no *Please go to #24*
 don't know *Please go to #24*

20a. What type of cancer was it?

_____ cancer

20b. When did your doctor first tell you that you had this type of cancer?

- age at diagnosis _____
or
year of diagnosis _____
 don't know

20c. Were you treated with radiation therapy (radiotherapy) for this cancer?

- yes
 no
 don't know

21. Has a doctor ever told you that you had any other cancer?

- yes
 no *Please go to #24*
 don't know *Please go to #24*

21a. What type of cancer was it?

_____ cancer

21b. When did your doctor first tell you that you had this type of cancer?

- age at diagnosis _____
or
year of diagnosis _____
 don't know

21c. Were you treated with radiation therapy (radiotherapy) for this cancer?

- yes
 no
 don't know

22. Has a doctor ever told you that you had any other cancer?

- yes
 no *Please go to #24*
 don't know *Please go to #24*

22a. What type of cancer was it?

_____ cancer

22b. When did your doctor first tell you that you had this type of cancer?

- age at diagnosis _____
or
year of diagnosis _____
 don't know

22c. Were you treated with radiation therapy (radiotherapy) for this cancer?

- yes
 no
 don't know

23. Has a doctor ever told you that you had any other cancer?

- yes
 no *Please go to #24*
 don't know *Please go to #24*

23a. What type of cancer was it?

_____ cancer

23b. When did your doctor first tell you that you had this type of cancer?

- age at diagnosis _____
or
year of diagnosis _____
 don't know

23c. Were you treated with radiation therapy (radiotherapy) for this cancer?

- yes
 no
 don't know

Medications

Have you ever taken any of the following medications regularly (at least twice a week for more than a month)?

24. Aspirin (such as Anacin, Bufferin, Bayer, Excedrin, Ecotrin)

- yes
 no *Please go to #25*
 don't know *Please go to #25*

24a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)?

Please choose one of the following.

- _____ times per day *or*
_____ times per week
 don't know

24b. About two years ago, were you taking it regularly?

- yes
 no
 don't know

24c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- _____ number of months *or*
_____ number of years
 don't know

Have you ever taken any of the following medications regularly (at least twice a week for more than a month)? . (continued)

25. Acetaminophen (such as Tylenol, Anacin-3, Panadol)
- yes
- no *Please go to #26*
- don't know *Please go to #26*

25a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)? *Please choose one of the following.*

- ___ times per day *or*
- ___ times per week
- don't know

25b. About two years ago, were you taking it regularly?

- yes
- no
- don't know

25c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months *or*
- ___ number of years
- don't know

26. Ibuprofen-based medications (such as Advil, Motrin, Nuprin, Medipren, Indocid, Naprosyn, NSAIDS (NSAIDS are non-steroidal anti-inflammatory drugs))

- yes
- no *Please go to #27*
- don't know *Please go to #27*

26a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)? *Please choose one of the following.*

- ___ times per day *or*
- ___ times per week
- don't know

26b. About two years ago, were you taking it regularly?

- yes
- no
- don't know

26c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months *or*
- ___ number of years
- don't know

Have you ever taken any of the following medications regularly (at least twice a week for more than a month)? (continued)

27. Bulk-forming laxatives (such as Metamucil, Citrucel, FiberCon, Serutan, psyllium)
- yes
- no *Please go to #28*
- don't know *Please go to #28*

27a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)? *Please choose one of the following.*

- ___ times per day *or*
- ___ times per week
- don't know

27b. About two years ago, were you taking it regularly? .

- yes
- no
- don't know

27c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months *or*
- ___ number of years
- don't know

28. Other laxatives (such as Ex-Lax, Correctol, Dulcolax, Senokot, Colace, castor oil, cod liver oil, mineral oil, milk of magnesia, lactulose, Epsom salts)
- yes
- no *Please go to #29*
- don't know *Please go to #29*

28a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)? *Please choose one of the following.*

- ___ times per day *or*
- ___ times per week
- don't know

28b. About two years ago, were you taking it regularly?

- yes
- no
- don't know

28c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months *or*
- ___ number of years
- don't know

Have you ever taken any of the following medications regularly (at least twice a week for more than a month)? (continued)

29. Multivitamin supplements (such as One-A-Day, Theragram, Centrum, Unicap) (not individual vitamins)

- yes
 no Please go to #30
 don't know Please go to #30

29a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)?

Please choose one of the following.

- ___ times per day or
___ times per week
 don't know

29b. About two years ago, were you taking it regularly?

- yes
 no
 don't know

29c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months or
___ number of years
 don't know

30. Folic acid or folate pills or tablets

- yes
 no Please go to #31
 don't know Please go to #31

30a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)?

Please choose one of the following.

- ___ times per day or
___ times per week
 don't know

30b. About two years ago, were you taking it regularly?

- yes
 no
 don't know

30c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months or
___ number of years
 don't know

Have you ever taken any of the following medications regularly (at least twice a week for more than a month)? (continued)

31. Calcium pills or tablets

- yes
 no Please go to #32
 don't know Please go to #32

31a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)?

Please choose one of the following.

- ___ times per day or
___ times per week
 don't know

31b. About two years ago, were you taking it regularly?

- yes
 no
 don't know

31c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months or
___ number of years
 don't know

32. Calcium-based antacids (such as Tums, Rolaids, Extra-strength Rolaids, Alka-Mints, Chooz Antacid gum)

- yes
 no *If female, please go to #33
If male, please go to #44*
 don't know *If female, please go to #33
If male, please go to #44*

32a. How often did you usually take it when you were taking it regularly (that is, at least twice a week for more than a month)?

Please choose one of the following.

- ___ times per day or
___ times per week
 don't know

32b. About two years ago, were you taking it regularly?

- yes
 no
 don't know

32c. How long, in total, have you taken this medication regularly? *If you started and stopped and then started again, please count only the time you were taking this medication.*

- ___ number of months or
___ number of years
 don't know

Men: please go to #44 on page 17

Women: please continue with #33 on page 13

Menstruation, Pregnancy, and Menopause

33. How old were you when you had your first menstrual period?
 ____ years of age
 don't know
 never had a menstrual period
34. Have you ever been pregnant?
 yes
 no ____.. Please go to #35
 don't know --Please go to #35
 How many times have you been pregnant? Please include miscarriages, stillbirths, tubal pregnancies and abortions.
 ____ number of pregnancies
 don't know
- 34a. How many times were you pregnant with more than one baby (twins, triplets or more)? If you are pregnant now, please do not include your current pregnancy.
 never
 ____ number of pregnancies with more than one baby
 don't know
- 34b. How many of your pregnancies lasted 6 months or longer? (Pregnancy usually lasts 9 months. Six months is about the earliest a baby could survive.) If you are pregnant now, please do-not include your current pregnancy.
 all of them
 ____ number of pregnancies lasting 6 months or longer
 don't know

- 34c. How many of your pregnancies resulted in live births?
 all of them
 ____ number of pregnancies with live-born children
 don't know
- 34d. How old were you at the first live birth?
 age at first birth ____ or
 year of first birth ____
 don't know
- 34e. How old were you at the last live birth?
 age at last birth ____ or
 year of last birth ____
 don't know
35. Have you ever used birth control pills or other hormonal contraceptives (implants or injections) for at least one year?
 yes
 no Please go to #36
 don't know Please go to #36
 How old were you when you first used any of these hormonal contraceptives?
 age at first use ____ or
 year of first use ____
 don't know
- 35a. Were you still using hormonal contraceptives about two years ago?
 yes
 no
 don't know

- 35b. In total, how long did you take these hormonal contraceptives? If you started and stopped and then started again, please count only the time you were taking these contraceptives.
 ____ number of years
 don't know
36. Have you had a menstrual period in the last 12 months? Please include only menstrual bleeding, not bleeding that results from hormone replacement therapy (HRT) or progesterones, progestins or withdrawal bleeding.
 yes Please go to #42
 don't know --Please go to #42
 Have your periods stopped permanently or only temporarily due to pregnancy, breast-feeding, or other conditions?
 permanently
 temporarily Please go to #42
37. How old were you when your periods stopped permanently?
 age they stopped ____ or
 year they stopped ____
 don't know
38. Why did your menstrual periods stop permanently? Please tick all that apply.
 natural menopause
 surgery
 radiation or chemotherapy
 other reason Please specify: _____
 don't know

- Please complete the next few questions which ask about surgeries you may have had. Please answer all questions.
39. Hysterectomy (only the uterus or womb removed)
 yes
 no
 don't know
 age when removed ____ or
 year when removed ____
- 39a. Hysterectomy with one ovary or part of an ovary removed
 yes
 no
 don't know
 age when removed ____ or
 year when removed ____
- 39b. Hysterectomy with both ovaries removed
 yes
 no
 don't know
 age when removed ____ or
 year when removed ____
- 39c. One ovary removed, completely or partly, without hysterectomy
 yes
 no
 don't know
 age when removed ____ or
 year when removed ____

39d. Both ovaries removed without hysterectomy
 yes
 no
 don't know
 age when removed ____ or
 year when removed _____
 don't know

40. Did you have radiation or chemotherapy, when
 1 you first have it?
 had radiation or chemotherapy
 age when this was given ____ or
 year when this was given _____
 don't know
 never had radiation or chemotherapy

41. If your periods stopped permanently for
 any reason other than surgery, radiation or
 chemotherapy, when did this occur?
 other reason _____
Please specify: _____
 age when occurred ____ or
 year when occurred _____
 don't know
 not applicable

42. Doctors prescribe hormone replacement
 therapy for many reasons, including
 menopausal symptoms, surgical removal of
 the ovaries, osteoporosis, and heart disease
 prevention. (Menopausal symptoms include
 hot flashes, sweating, and depression.)

Have you ever taken hormone replacement
 therapy prescribed by a doctor and in the form
 of a pill or a patch?

*Please do not include hormone therapy that
 was prescribed for birth control, infertility,
 hormone therapy delivered by injections,
 vagina creams or vaginal suppositories, or
 herbal or soy products.*

yes
 no *Please go to #43*
 don't know *Please go to #43*

42a. Were you still having menstrual
 periods when you first took these
 hormones?
 yes
 no
 don't know

42b. Were you prescribed either an estrogen-only
 pill or patch (such as Premarin) for hormone
 replacement therapy?

yes
 no
 don't know

How old were you when you first
 took estrogen-only medication?

age when first taken ____ or
 year when first taken _____

don't know

42c. Were you still using estrogen-only
 medication for hormone replacement therapy
 about two years ago?

yes
 no
 don't know

42d. In total, how long did you take
 estrogen-only medication for hormone
 replacement therapy? *If you started and
 stopped and then started again, please
 count only the time you were taking this
 medication.*

_____ number of months or

_____ number of years

don't know

42e. Progesterone or progestin is frequently
 prescribed by doctors together with estrogen
 for hormone replacement therapy. One
 common brand name is Provera. Another one
 is Prometrium. Have you ever taken
 progesterone or progestin together with
 estrogens for hormone replacement therapy?

yes
 no *Please go to #43*
 don't know *Please go to #43*

How old were you when you first
 took progesterone or progestin
 together with estrogens?

age when first taken ____ or
 year when first taken _____

don't know

42f. Were you still using progesterone or
 progestin medication about two years
 ago?

yes
 no
 don't know

42g. In total, how long did you take progesterone
 or progestin together with estrogens? *If you
 started and stopped and then started again,
 please count only the time you were taking
 this medication.*

_____ number of months or
 _____ number of years

don't know

43. Have you ever taken tamoxifen, raloxifene,
 or other anti-estrogen medication (such as
 Lupron or Depo-Provera)?

yes
 no *Please go to #44*
 possibly - I have participated in a
 clinical trial for tamoxifen or other
 anti-estrogen medication
 don't know *Please go to #44*

What anti-estrogen medication did you
 take? *Please tick all that apply.*

tamoxifen
 raloxifene
 other: _____
please specify

43a. How old were you when you first
 took tamoxifen, raloxifene or other
 anti-estrogen medication?

age when first taken ____ or
 year when first taken _____

don't know

43b. Were you still taking tamoxifen, raloxifene
 or other anti-estrogen medication about two
 years ago?

yes
 no
 don't know

43c. In total, how long did you take tamoxifen,
 raloxifene or other anti-estrogen medication?
*If you started and stopped and then started
 again, please count only the time you were
 taking this medication.*

_____ number of months or

_____ number of years

don't know

Diet

44. About two years ago, on average, how often did you eat a piece or serving of fruit?
 (A serving of fruit is: 1 medium-sized fresh fruit; 1/2 cup of chopped, cooked or canned fruit; 1/4 cup of dried fruit; 6 ounces of fruit juice (50%-100% pure juice).) *Please choose one of the following.*
 ___ servings per day *or*
 ___ servings per week *or*
 ___ servings per month
 don't know
45. About two years ago, on average, how often did you eat a serving of vegetables? *Please include green salads, beans, lentils, etc., and potatoes (not packaged potato chips).*
 (A serving of vegetables is: 1 cup raw leafy vegetables; 1/2 cup of other vegetables, cooked or chopped raw; 6 ounces of vegetable juice.) *Please choose one of the following.*
 ___ servings per day *or*
 ___ servings per week *or*
 ___ servings per month
 don't know
46. About two years ago, on average, how often did you eat a serving of red meat (not chicken or fish)?
 (A serving of red meat is: 2-3 ounces of red meat (a piece of meat about the size of a deck of cards). Red meats include: beef, steak, hamburger, prime rib, ribs, beef hot dogs, beef-based processed meat, veal, pork, bacon, pork sausage, ham, lamb, venison.) *Please choose one of the following.*
 ___ servings per day *or*
 ___ servings per week *or*
 ___ servings per month
 didn't eat red meat *Please go to #47*
 don't know
- 46a. About two years ago, on average, how often did you eat a serving of red meat that was cooked by broiling, grilling, barbecuing or pan-frying (not stir-fried or deep-fried)? *Please choose one of the following.*
 ___ servings per day *or*
 ___ servings per week *or*
 ___ servings per month
 didn't eat red meat that was cooked by these methods *Please go to #47*
 don't know

- 46b. On average, when you ate red meat cooked by these methods, which of the following best describes its appearance?
- | | |
|--|--|
| What was its outside appearance? | What was its inside appearance (how well done it was)? |
| <input type="radio"/> lightly browned | <input type="radio"/> red (rare) |
| <input type="radio"/> medium browned | <input type="radio"/> pink (medium) |
| <input type="radio"/> heavily browned or blackened | <input type="radio"/> brown (well-done) |
| <input type="radio"/> don't know | <input type="radio"/> don't know |
47. About two years ago, on average, how often did you eat a serving of chicken? *Please do not include turkey or any other bird.*
 (A serving of chicken is: 2-3 ounces of chicken meat; 1 drumstick; 1 thigh; half a breast; 2 wings; 3 nuggets.) *Please choose one of the following.*
 ___ servings per day *or*
 ___ servings per week *or*
 ___ servings per month
 didn't eat chicken *Please go to #48*
 don't know
- 47a. About two years ago, on average, how often did you eat a serving of chicken that was cooked by broiling, grilling, barbecuing or pan-frying (not stir-fried or deep-fried)? *Please choose one of the following.*
 ___ servings per day *or*
 ___ servings per week *or*
 ___ servings per month
 didn't eat chicken that was cooked by these methods *Please go to #48*
 don't know
- I
 J 47b. On average, when you ate chicken cooked by these methods, which of the following best describes its appearance?
- | | |
|--|---|
| What was its outside appearance? | |
| <input type="radio"/> lightly browned | † |
| <input type="radio"/> medium browned | |
| <input type="radio"/> heavily browned or blackened | |
| <input type="radio"/> don't know | |

Physical Activity

We would like you to think back to when you were in your 20s and remember the physical activities you participated in then.

48. In your 20s, did you participate regularly in physical activity for a total of at least 30 minutes a week? Please describe your activities below.

		For how many years?	During those years, for how many months per year?	During those months, on average, for how many minutes or hours per week?
Walking	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Jogging (running slower than a mile in 10 minutes)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Running (running faster than a mile in 10 minutes)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Bicycling (including using an exercise bicycle)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Swimming laps	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Tennis, squash, racquetball	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Calisthenics, aerobic, vigorous dance (including ballet), using a rowing machine, lifting weights	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Football, soccer, rugby, basketball	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
Heavy household work (examples: using a non-power mower, shoveling, moving heavy loads, scrubbing floors)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week

In your 20s, did you do any other strenuous activities? Strenuous activity means something that really increased your heart rate, made you hot, and caused you to sweat. Some examples are: skiing, skating, hockey, hunting, sledding or tobogganing, water-skiing.

Activity please specify	For how many years?	During those years, for how many months per year?	During those months, on average, for how many minutes or hours per week?
_____	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
_____	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
_____	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
_____	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
_____	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week
_____	___ years	___ months	___ minutes per week <i>or</i> ___ hours per week

49. When you were in your 20s, what was your usual occupation? (We mean what you did for the longest time, including any paid or unpaid employment, such as being a student or housewife or being unemployed.)

_____ occupation

don't know

If you are younger than age 31, please go to the next section (Alcohol Consumption) on page 25. Otherwise, please continue with #50.

Now, please think back to your 30s and 40s.

50. In your 30 and 40s, did you participate regularly in physical activity for a total of at least 30 minutes a week? Please describe your activities below.

		For how many years?	During those years, for how many months per year?	During those months, on average, for how many minutes or hours per week?
Walking	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Jogging (running slower than a mile in 10 minutes)	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Running (running faster than a mile in 10 minutes)	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Bicycling (including using an exercise bicycle)	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Swimming laps	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Tennis, squash racquetball	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Calisthenics, aerobics, vigorous dance (including ballet), using a rowing machine, lifting weights	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Football, soccer rugby, basketball	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
Heavy household work (examples: using a non-power mower, shoveling, moving heavy loads, scrubbing floors)	<input type="radio"/> yes <input type="radio"/> no	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week

In your 30s and 40s, did you do any other strenuous activities? ~~is~~ something that really increased your heart rate, made you hot, and caused you to sweat. Some examples are: skiing, skating, hockey, hunting, sledding or tobogganing, water-skiing.

Activity <i>please specify</i>	For how many years?	During those years, for how many months per year?	During those months, on average, for how many minutes or hours per week?
_____	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
_____	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
_____	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
_____	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week
_____	____ years	____ months	____ minutes per week <i>or</i> ____ hours per week

51. When you were in your 30s and 40s, what was your usual occupation? (We mean what you did for the longest time, including any paid or unpaid employment, such as being a student or housewife or being unemployed.)

_____ occupation †
 don't know

If you are younger than age 51, please go to the next section (Alcohol Consumption) on page 25. Otherwise, please continue with #52.

-Now, please think back to since you turned 50.

52. Since you turned 50, did you participate regularly in physical activity for a total of at least 30 minutes a week? Please describe your activities below.

		For how many years?	During those years, for how many months per year?	During those months, on average, for how many minutes or hours per week?
Walking	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Jogging (running slower than a mile in 10 minutes)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Running (running faster than a mile in 10 minutes)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Bicycling (including using an exercise bicycle)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Swimming laps	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Tennis, squash racquetball	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Calisthenics, aerobics, vigorous dance (including ballet), using a rowing machine, lifting weights	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Football, soccer rugby, basketball	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week
Heavyhousehold work (examples: using a non-power mower, shoveling, moving heavy loads, scrubbing floors)	<input type="radio"/> yes <input type="radio"/> no	___ years	___ months	___ minutes per week or ___ hours per week

Since you turned 50, did you do any other strenuous activities? Strenuous activity means something that really increased your heart rate, made you hot, and caused you to sweat. Some examples are: skiing, skating, hockey, hunting, sledding or tobogganing, water-skiing.

Activity please specify	For how many years?	During those years, for how many months per year?	During those months, on average, for how many minutes or hours per week?
_____	___ years	___ months	___ minutes per week or ___ hours per week
_____	___ years	___ months	___ minutes per week or ___ hours per week
_____	___ years	___ months	___ minutes per week or ___ hours per week
_____	___ years	___ months	___ minutes per week or ___ hours per week
_____	___ years	___ months	___ minutes per week or ___ hours per week
_____	___ years	___ months	___ minutes per week or ___ hours per week

53. Since you turned 50, what was your usual occupation? (We mean what you did for the longest time, including any paid or unpaid employment, such as being a student or housewife or being unemployed.)

_____ occupation
 don't know



Alcohol Consumption

We would like you to think back to when you were in your 20s.

54. In your 20s, did you ever consume any alcoholic beverages at least once a week for 6 months or longer? *Please describe your consumption below.*

	For how many years?	During those years, how much did you typically consume?
3% alcohol) <input type="radio"/> don't know		<input type="radio"/> per day
Beer, hard <input checked="" type="radio"/> yes cider (at least <input type="radio"/> no	____ years consumed	____ number of 12 ounce cans or bottles
		<input type="radio"/> per week
		<input type="radio"/> don't know
Wine <input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	____ years consumed	____ number of 4 ounce glasses of wine
		<input type="radio"/> per day
		<input type="radio"/> per week
		<input type="radio"/> don't know
Sake, sherry, port <input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	____ years consumed	____ number of 1 ounce servings
		<input type="radio"/> per day
		<input type="radio"/> per week
		<input type="radio"/> don't know
Spirits, liquor mixed drinks, brandy, liqueurs <input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	____ years consumed	____ number of 1 ounce shots liquor or spirits
		<input type="radio"/> per day
		<input type="radio"/> per week
		<input type="radio"/> don't know

55. When you were in your 20s, how many years in total did you consume at least one alcoholic beverage (of any type) a week?

____ years consumed

never consumed alcohol

56. On average, how many alcoholic beverages a week did you consume during those years? That is, how many 4 ounce glasses of wine or 12 ounce cans or bottles of beer or hard cider, or 1 ounce servings of sake, sherry, port, or spirits, mixed drinks and cocktails.

____ number of alcoholic beverages a week

never consumed alcohol

If you are younger than age 31, please go to the next section (Smoking) on page 28. Otherwise, please continue with #57.

Now, please think back to your 30s and 40s.

57. In your 30s and 40s, did you ever consume any alcoholic beverages at least once a week for 6 months or longer? *Please describe your consumption below.*

	For how many years?	During those years, how much did you typically consume?
Beer, hard <input type="radio"/> yes	____ years consumed	____ number of 12 ounce
		<input type="radio"/> per day
cider (at least <input type="radio"/> no		____ cans or bottles
3% alcohol) <input type="radio"/> don't know		<input type="radio"/> per day <input type="radio"/> per week <input type="radio"/> don't know
Wine <input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	____ years consumed	____ number of 4 ounce glasses of wine
		<input type="radio"/> per day
		<input type="radio"/> per week
		<input type="radio"/> don't know
Sake, sherry, port <input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	____ years consumed	____ number of 1 ounce servings
		<input type="radio"/> per day
		<input type="radio"/> per week
		<input type="radio"/> don't know
Spirits, liquor mixed drinks, brandy, liqueurs <input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	____ years consumed	____ number of 1 ounce shots liquor or spirits
		<input type="radio"/> per day
		<input type="radio"/> per week
		<input type="radio"/> don't know

58. When you were in your 30s and 40s, how many years in total did you consume at least one alcoholic beverage (of any type) a week?

____ years consumed

never consumed alcohol

59. On average, how many alcoholic beverages a week did you consume during those years? That is, how many 4 ounce glasses of wine or 12 ounce cans or bottles of beer or hard cider, or 1 ounce servings of sake, sherry, port, or spirits, mixed drinks and cocktails.

____ number of alcoholic beverages a week

never consumed alcohol

If you are younger than age 51, please go to the next section (Smoking) on page 28. Otherwise, please continue with #60.

Now, please think back to since you turned 50.

60. Since you turned 50, did you ever consume any alcoholic beverages at least once a week for 6 months or longer? *Please describe your consumption below.*

		For how many years?	During those years, how much did you typically consume?
Beer, hard cider (at least 3% alcohol)	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	_____ years consumed	_____ number of 12 ounce cans or bottles <input type="radio"/> per day <input type="radio"/> per week <input type="radio"/> don't know
Wine	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	_____ years consumed	_____ number of 4 ounce glasses of wine <input type="radio"/> per day <input type="radio"/> per week <input type="radio"/> don't know
Sake, sherry, port	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	_____ years consumed	_____ number of 1 ounce servings <input type="radio"/> per day <input type="radio"/> per week <input type="radio"/> don't know
Spirits, liquor mixed drinks, brandy, liqueurs	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	_____ years consumed	_____ number of 1 ounce shots liquor or spirits <input type="radio"/> per day <input type="radio"/> per week <input type="radio"/> don't know

61. Since you turned 50, how many years in total did you consume at least one alcoholic beverage (of any type) a week?

_____ years consumed
 never consumed alcohol

62. On average, how many alcoholic beverages a week did you consume during those years? That is, how many 4 ounce glasses of wine or 12 ounce cans or bottles of beer or hard cider, or 1 ounce servings of sake, sherry, port, or spirits, mixed drinks and cocktails.

_____ number of alcoholic beverages a week
 never consumed alcohol

Smoking

63. Have you ever smoked at least one cigarette a day for 3 months or longer?

yes
 no *Please go to #64*
 don't know *Please go to #64*

63a. When did you first start smoking at least one cigarette a day?

age at first use _____ or
year of first use

don't know

63b. During periods when you smoked regularly, how many cigarettes did you typically smoke in a day?

_____ cigarettes per day
 don't know

63c. About two years ago, were you still smoking at least one cigarette a day?

yes
 no
 don't know

63d. Do you still smoke at least one cigarette a day?

yes *Please go to #63f*
 no *Please go to #63e*
 don't know

63e. When did you stop smoking at least one cigarette a day (we mean stop smoking permanently)?

age at last use _____ or
year of last use

don't know

63f. How many years, in total, did you smoke at least one cigarette a day for 3 months or longer? (If you have stopped and restarted at least once, count only the time when you were smoking.)

_____ total number of years
 don't know

64. Have you ever smoked at least one cigar a month for at least 3 months?

yes
 no *Please go to #65*
 don't know *Please go to #65*

64a. When did you first start smoking at least one cigar a month?

age at first use _____ or
year of first use

don't know

64b. During periods when you smoked regularly, how many cigars did you typically smoke in a month?

_____ cigars per month
 don't know

64c. About two years ago, were you still smoking at least one cigar a month?

yes
 no
 don't know

64d. Do you still smoke at least one cigar a month?

yes *Please go to #64f*
 no *Please go to #64e*
 don't know

64e. When did you stop smoking at least one cigar a month (we mean stop smoking permanently)?

age at last use _____ or
year of last use

don't know

64f. How many years, in total, did you smoke at least one cigar a month for 3 months or longer? (If you have stopped and restarted at least once, count only the time when you were smoking.)

_____ total number of years
 don't know

65. Have you ever smoked at least one pipe a month for at least 3 months?

- yes
- no *Please go to #66*
- don't know *Please go to #66*

65a. When did you first start smoking at least one pipe a month?

age at first use _____ or
year of first use

don't know

65b. During periods when you smoked regularly, how many pipes did you typically smoke in a month?

_____ pipes per month
 don't know

65c. About two years ago, were you still smoking at least one pipe a month?

- yes
- no
- don't know

65d. Do you still smoke at least one pipe a month?

- yes *Please go to #65/*
- no *Please go to #65e*
- don't know

65e. When did you stop smoking at least one pipe a month (we mean stop smoking permanently)?

age at last use _____ or
year of last use

don't know

65f. How many years, in total, did you smoke at least one pipe a month for 3 months or longer? (*If you have stopped and restarted at least once, count only the time when you were smoking.*)

_____ total number of years
 don't know

Height and Weight

66. About how tall are you, without your shoes on?

___ feet ___ inches

or

_____ centimetres

don't know

67. How much did you weigh about two years ago?

___ pounds

or

_____ kilograms

don't know

68. How much did you weigh when you were about 20 years old?

___ pounds

or

_____ kilograms

don't know

Additional Information

69. Previous to this study, have you and your relatives ever taken part in any family health studies?

yes

no

don't know

Background Information

70. What is the highest level of education that you completed?

- less than 8 years
- 8 to 11 years
- high school graduate
- vocational or technical school
- some college or university
- bachelor's degree
- graduate degree
- don't know

71. Country of birth sometimes affects disease risk. Please fill in country of birth for yourself, your parents and your grandparents.

In addition, scientists have found that some genetic traits are more common or less common among Jewish people of different ethnic backgrounds. Please answer the questions about Jewish descent for each person.

	Country of birth	Is this person of Jewish descent?	Ashkenazi (East European)	Sephardic	other	don't know
You	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your mother	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your father	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your mother's mother	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your mother's father	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your father's mother	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your father's father	_____	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

72. How many years have you lived in Canada?

- all my life
- ___ number of years
- don't know

73. Ethnicity and race sometimes affect disease risk. Scientists have found that some genetic traits are more common or less common among people of different backgrounds. We would like to know if this is true for genes associated with colorectal cancer.

Please fill in the background for yourself, your parents and your grandparents.
Please tick all that apply.

	<i>You</i>	Your mother	Your father	Your mother's mother	Your mother's father	Your father's mother	Your father's father
Black, from Africa	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Black, from the Caribbean (e.g. Trinidad, Jamaica, Haiti)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Black, from North America	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Black, other	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
White	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
First Nations (e.g. Indian, Inuit)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
North African (e.g. Egyptian)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Middle Eastern (e.g. Iranian)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Filipino	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Japanese	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Korean	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chinese	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other South East Asian (e.g. Vietnamese)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
South Asian (e.g. East Indian, Pakistani)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
other: please specify	_____	_____	_____	_____	_____	_____	_____
don't know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

74. Which of the following categories best describes your total annual household income about two years ago?

- no income
- less than \$6,000
- \$6,000 - \$11,999
- \$12,000 - \$19,999
- \$20,000 - \$29,999
- \$30,000 - \$39,999
- \$40,000 - \$49,999
- \$50,000 - \$59,999
- \$60,000 - \$69,999
- \$70,000 - \$79,999
- \$80,000 or more
- don't know

75. In case we need to contact you in the future and you have moved, could we have the name of someone who is not living with you to whom we might write or call for your new address?

Name of relative or friend: _____

Your relationship: _____

His or her address: _____

His or her telephone number: (____) ____ - ____ - ____

Thank you very much for taking the time to fill out this questionnaire.
We appreciate your participation.

Please mail this completed questionnaire in the return envelope provided.

APPENDIX 2

Example of Imputation Methods Used for Physical Activity Variables

APPENDIX 2. EXAMPLE OF IMPUTATION METHODS USED FOR PHYSICAL ACTIVITY VARIABLES

The two tables below demonstrates all possible missing physical activity patterns, using walking during the 20s as an example. Participants were asked, ‘in your 20s, did you participate regularly in physical activity for a total of at least 30 minutes per week? Please describe your activities below’. Upon cross tabulations, we can identify the patterns among those who responded, ‘yes’, ‘no’, and participants who did not respond, thus leaving the associated field blank. In this example, 51 participants left every walking field blank. An assumption was made that these participants did not perform the activity, and as such left each field blank. Similarly, 91 participants said they walked, but when asked further details related to frequency and time, the fields were missing and another assumption was made these participants did not walk during this age period. A total of 391 participants reported they did not walk during their 20s, therefore the rest of the fields were appropriately skipped. A second table illustrates the effect of imputation on the proportion of individuals who report no walking during their 20s. Following imputation, 533 participants were reported not walking during their 20s. This is a considerable difference, demonstrating the impact of imputations on physical activity distributions. All other imputation methods and the rationale for their use are listed below.

Walking during the 20s missing patterns pre-imputations								
Walk (Y/N)	Hours/ week	Minutes/ week	months/ year	years/ timeframe	Freq	%	Impute (Y/N)	Imputation methods/rationale ¹²
Missing	Missing	Missing	Missing	Missing	51	3.66	Y	Assumed activity was not performed; '0' will be imputed for walking
Missing	Not Missing	Missing	Missing	Not Missing	1	0.07	Y	Activity was performed; '1' will be imputed for walking; mean value for mpy will be imputed
Y	Missing	Missing	Missing	Missing	91	6.52	Y	Assumed activity was not performed; '0' will be imputed for walking
Y	Missing	Missing	Missing	Not Missing	13	0.93	N	More than one field missing; Walking METs will remain missing;
Y	Missing	Missing	Not Missing	Missing	12	0.86	N	More than one field missing; Walking METs will remain missing;
Y	Missing	Missing	Not Missing	Not Missing	39	2.8	Y	Median value for hours/week will be imputed
Y	Missing	Not Missing	Missing	Missing	2	0.14	N	More than one field missing; Walking MET--hrs will remain missing
Y	Missing	Not Missing	Missing	Not Missing	2	0.14	Y	Mean value for months /year will be imputed
Y	Missing	Not Missing	Not Missing	Missing	1	0.07	Y	Mean value for years will be imputed
Y	Missing	Not Missing	Not Missing	Not Missing	33	2.37	N	No missing values
Y	Not Missing	Missing	Missing	Missing	16	1.15	N	More than one field missing; Walking MET--hrs will remain missing
Y	Not Missing	Missing	Missing	Not Missing	12	0.86	Y	Mean value for months/ year will be imputed
Y	Not Missing	Missing	Not Missing	Missing	17	1.22	Y	Mean value for years will be imputed
Y	Not Missing	Missing	Not Missing	Not Missing	654	46.9	N	No missing values
Y	Not Missing	Not Missing	Missing	Missing	3	0.22	N	More than one field missing; Walking MET-hrs will remain missing;
Y	Not Missing	Not Missing	Missing	Not Missing	3	0.22	Y	Mean value for months /year will be imputed
Y	Not Missing	Not Missing	Not Missing	Missing	1	0.07	Y	Mean value for years will be imputed
Y	Not Missing	Not Missing	Not Missing	Not Missing	53	3.8	N	No missing values
N	Missing	Missing	Missing	Missing	391	28.0	N	No missing values

¹ Imputations = 218; Missing = 46; No walking (pre-imputations) =391; mpy=months per year

²If more than one physical activity field were missing, walking MET--hours would remain missing. Imputations using mean or median were for observations with only one missing physical activity field. Imputations are defined as any change to data for the purpose of correcting potential errors, or imputing a mean or median value for missing data

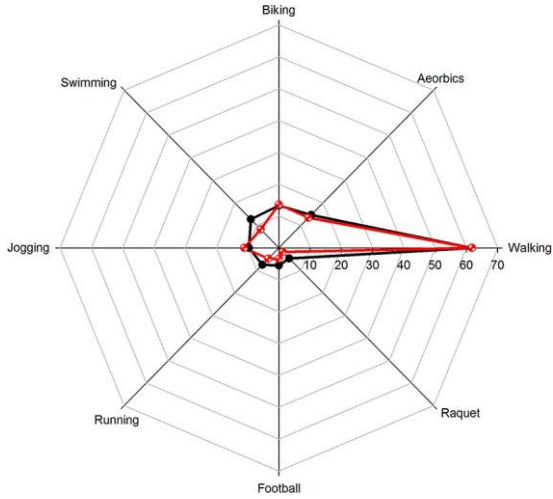
Walking during the 20s post-imputations¹							
Walking (Y/N)	Hours/week	Minutes/week	Months/year	Years/timeframe	Freq.	%	Cumulative Freq.
Y	Missing	Missing	Missing	Not Missing	13	0.93	13
Y	Missing	Missing	Not Missing	Missing	12	0.86	25
Y	Missing	Not Missing	Missing	Missing	2	0.14	27
Y	Missing	Not Missing	Not Missing	Not Missing	36	2.58	63
Y	Not Missing	Missing	Missing	Missing	16	1.15	79
Y	Not Missing	Missing	Not Missing	Not Missing	723	51.83	802
Y	Not Missing	Not Missing	Missing	Missing	3	0.22	805
Y	Not Missing	Not Missing	Not Missing	Not Missing	57	4.09	862
N	Missing	Missing	Missing	Missing	533	38.21	1395

¹No walking (post-imputations) = 533; Missing = 46

APPENDIX 3

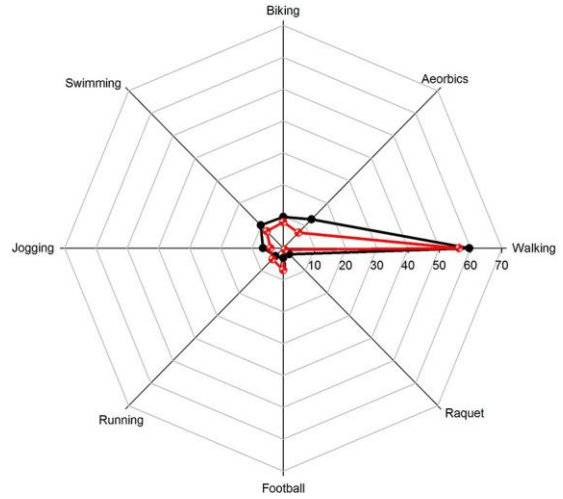
The Distribution of Close-Ended Physical Activities per Age Period Using Radar Graphs

PA profile. closed ended questions
Cases vs Controls, age 20-29



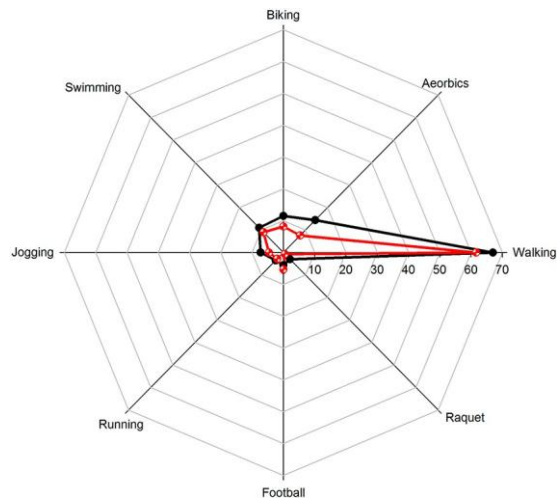
— Controls
⋯ Cases

PA profile. closed ended questions
Cases vs Controls, age 30-49



— Controls
⋯ Cases

PA profile. closed ended questions
Cases vs Controls, age 50 and over



— Controls
⋯ Cases