PHYSICAL ACTIVITY, THE DIRECT AND INDIRECT EFFECT OF SOCIOECONOMIC STATUS ON RISK FACTORS OF COLORECTAL CANCER IN CANADA

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Physical activity, the direct and indirect effect of socioeconomic status on risk factors of colorectal cancer in Canada

by

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Abstract

The objective of this thesis was to examine the determinants of colorectal cancer (CRC) from two perspectives: 1) the associations between recreational physical activity and the risk of CRC; 2) the direct and indirect effect of socioeconomic status on the risk of CRC.

Higher levels of physical activity have been consistently associated with lower risk of CRC in previous studies. Nevertheless, the specific mode, intensity, frequency, and duration of physical activity required for CRC prevention are not well known and remain controversial. The first objective of this study is to examine the associations of walking, non-walking exercise, and total recreational physical activity on colorectal cancer development. The study used the data collected from the existing population based case-control study of Ontario (ON) and Newfoundland and Labrador (NL), in which personal history, life style and dietary information were collected using the Personal History Questionnaire (PHQ), Food Frequency Questionnaire (FFQ) and Family History Questionnaire (FHQ). Multivariable logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence interval (95%CI) after adjusting potential confounding covariates. Pooled analysis in both ON and NL was also conducted. Results from this study showed that the highest quintile of walking was associated with increased colorectal cancer risk for both males and females in both provinces (highest VS lowest: ON: OR=1.51, 95%CI=1.07-2.13; NL: OR=2.01, 95%CI=1.25-3.22; pooled analysis: OR=1.70, 95%CI=1.09-2.66). However, this result could be biased because a higher proportion of cases responded to this item than controls. Non-walking exercise was insignificantly associated with a reduced risk of colorectal cancer for both sexes and provinces. These findings suggested that increasing amounts of neither walking nor non-walking exercise was associated with reducing the risk of colorectal cancer. More specified prospective studies on physical activity are needed to evaluate effective frequency, duration and intensity of physical activity in relation to colon and rectal cancer prevention.

Existing epidemiologic studies have not investigated how risk factors work together to increase the incidence of CRC; therefore, the true effect of each factor could be under- or over- estimated. The second component of this thesis was to explore how socio-economic status (SES) directly influences the risk of developing CRC and its mediated effect on CRC risk through diet while adjusting for possible risk factors of alcohol intake, smoking, physical inactivity, and obesity. Using the data from just the NL province, measurement and structural modeling was used to test conceptual models. Exploratory factor analysis was used to identify dietary patterns measured by 39 food groups. Next, the direct and intermediate effects of risk factors were examined using structural equation modeling. The results from multivariable regression analysis indicated that age (OR=1.03), SES (OR=0.89), processed meat intake (OR=1.08), non-screening (OR=2.67), smoking (OR=1.44, 1.85 (ever, current)), and family history score of CRC (OR=1.06), were significantly associated with the risk of CRC. SES (β=0.05) has a direct effect on the risk of CRC and the indirect effect (β=0.06) of SES on the risk of CRC also appeared to exist through processed meat intake (β=0.01), lower vegetable intake (β=0.01), lower screening frequency (β=0.02), and smoking (β=0.02). This study indicated that the NL population has three major dietary patterns. Also, structural equation modeling used in this study, a relatively new approach in epidemiology studies, provided unique information of the direct effect of SES on the development of CRC and its indirect effects through a set of candidate CRC risk factors.

KEY WORDS

Colorectal cancer, physical activity, socioeconomic status, diet pattern, direct effect, indirect effect.

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Glossary

Comparative Fit Index (CFI): also known as the Bentler Comparative Fit Index. CFI is considered as improvement in noncentrality (from the null to the hypothesized model) to the noncentrality of the null model in which assumes that no interrelationships among any of the variables (*independence model* or *null model*). A recommended value of CFI is 0.9 or above [1, 2].

Direct Effects: the effect that goes directly from one variable to a second variable [3].

Exploratory Factor Analysis (EFA): it is a statistical method used to explore the dimensionality (factors/latent variables) of a measurement model by finding the smallest number of interpretable factors to explain the correlation among a set of variables [4].

Factor Loading: The correlation of the measured variable and its factor, with higher loadings make the variable representative of the factor. Factor loadings greater than 0.3 are considered to meet the minimal level; loadings of 0.4 are considered more important; and if the loadings are 0.5 and greater, they are considered practically significant [5].

Goodness of Fit: How well a hypothesized or theoretical model, a distribution, or an equation fits actual data [6].

Goodness of Fit Index: a measure of the proportion of variance and covariance that the hypothesized or theoretical model is able to explain [6, 7].

Indicators: also called *observed variables*, *measured variables*, or *manifest variables*. Actual measured value for a specific item or question, obtained either from respondents in response to questions or from observations by a researcher, which can be directly measured. Indicators are represented by squares or rectangles. By convention, indicators should have pattern coefficients (factor loadings) of 0.3 or higher on their latent factors.

Indirect Effects: the effects between two variables that are mediated by one more mediating

variables [3].

Latent Variables: also called *factors*, *constructs* or *unobserved variables*. The main characteristic of latent variables is that they cannot be directly observed or measured; it hypothetically exists in a study to explain variables that can be observed or measured. They are measured by a set of observed variables. Latent variables are represented by circles or ovals [8].

Mediating Variable: A variable occurs in a casual pathway from an independent to a dependent variable. It causes variation in the dependent variables but also it is influenced by the variation of the independent variables. Synonyms are intervening variable, mediator variable, intermediate variable, and contingent variable [9].

Normed Fit Index (NFI) or Non-normed fit index (NNFI): also known as Tucker-Lewis Index, the chi-square value of the null model is compared to that of a proposed model. A recommended value of NFI and NNFI is 0.9 or higher [1, 2].

Root Mean Square Error of Approximation (RMSEA): a measure of the discrepancy per degree of freedom in the model. Values less than 0.05 or 0.06 indicate reasonable fit [1, 2].

Structural Equation Modeling (SEM): Structural equation modeling is a multivariate technique incorporating multiple regression (examining dependence relationships) and factor analysis (representing observed (measured) and unobserved (latent factors) variables) to estimate the direct and indirect relationships of measured variables and latent factors [10].

Weighted Root Mean Square Residual (WRMR): This is a relatively new fit index that is believed to be better suite categorical data. WRMR values less than 1.0 depict a good fitting model [1, 2].

Abbreviations

BMI	Body Mass Index
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
CRC	Colorectal Cancer
EFA	Exploratory Factor Analysis
FFQ	Food Frequency Questionnaire
FHQ	Family History Questionnaire
HRT	Hormone Replacement Therapy
ICD	International Classification of Disease
NFCCR	Newfoundland Familial Colorectal Cancer Registry
NFI	Normed Fit Index
NL	Newfoundland and Labrador
NNFI	Non-normed Fit Index
NOCS	Newfoundland and Ontario Colorectal Cancer Study
NSAID	Nonsteroidal Anti-inflammatory Drug
OFCCR	Ontario Familial Colorectal Cancer Registry
ON	Ontario
OR	Odds Ratios
PHQ	Personal History Questionnaire
RMSEA	Root Mean Square Error of Approximation
SEM	Structural Equation Modeling
SES	Socio-economic Status
WRMR	Weighted Root Mean Square Residual

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Chapter 1 Introduction

1.1 Background

Colorectal cancer (CRC) has become a health problem of increasing significance in Canada, with an estimated 22,500 new cases and 9,100 deaths in 2010 [11]. CRC is the third most common type of cancer among Canadian males and females [11]. The province of Newfoundland and Labrador (NL) has the highest age-standardized incidence rate of CRC in Canada at 86/100,000 [11]; indeed, this is one of the highest incidence rates of CRC in the world. Ontario experiences the average Canadian incidence rate at 51/100,000 [11].

Physical activity has long been considered an effective strategy for cancer prevention [12]. Comprehensive reviews found that increased physical activity is a substantial protective factor against colon or colorectal cancer [13-16]. Numerous prospective [17-20] and case-control [21, 22] studies have found statistically significant associations between physical activity and colon cancer, especially for men. Few studies of rectal cancer indicated no associations [23-25]. The measurement of physical activity in these studies varied and was based upon limited types of activity. The type, frequency, duration and intensity of physical activity are all important to reduce risk of colorectal cancer [12, 26]; however, this kind of information is limited. In Canada, few studies have focused on examining the relationships between specific physical activity and colorectal cancer risk, especially in a large population.

Epidemiological research to date has suggested that a wide range of environmental and lifestyle factors such as dietary factors, physical inactivity, smoking, alcohol consumption and socioeconomic status may contribute to the increased incidence of CRC; however, most of the results have been inconsistent [27-36]. The World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) second expert report classified risk factors

into four major groups according to the strength of the evidence. Physical activity, consumption of red meat, or processed meat, excessive alcohol drinking (above 30g/day), body and abdominal fatness, and adult attained height are convincing risk factors of CRC; intakes of dietary fibre, garlic, milk and calcium probably reduce CRC risk; non-starchy vegetables, fruits, folate, selenium, fish and vitamin D have limited suggestive evidence of declining CRC risk; while intakes of iron, cheese, food containing animal fat, and sugars have limited but inconclusive evidence of raising CRC risk.

A large number of epidemiological studies have focused on examining major risk factors of interest while controlling for other covariates. This oversimplifies the complicated, interdependent relationships among various factors of interest [37]. Consequently, most reported studies have been unable to specify how variables work together to give rise to CRC and tend to under-estimate the true effect of each factor [38-40]. Therefore, studies that are able to delineate and test how various factors are interrelated and jointly affect outcomes would be expected to provide important insights into CRC etiology. Although the inter-dependent relationships among socioeconomic status (SES), lifestyles, diet, and health are well recognized [41-43], their complex inter-relationships in relevance to CRC have not been examined. We hypothesized that lower SES predisposes people to certain risk factors (e.g. poor dietary intake, smoking, alcohol consumption and obesity), which in turn may interact with genetic factors and lead to the development of colorectal cancer. A large population-based Newfoundland and Ontario Colorectal cancer Study (NOCS) was expected to provide valuable insights on the risk factors of CRC and potential prevention strategies for this disease.

1.2 Objectives

The objective of the first component of this thesis was to examine the association between colorectal cancer risk and several types of physical activity (walking, non-walking exercise and total physical activity).

The second component of this thesis was to achieve the following specific objectives: 1) explore the potential association among risk factors of colorectal cancer; 2) posit a conceptual model that delineates the inter-relationships with respect to how SES, dietary factors, and lifestyle factors work together to give rise to CRC; 3) operationalize the proposed conceptual model using the database of Newfoundland and Ontario Colorectal-cancer Study (NOCS). It is important to note that only the NL data was used in the second component of this thesis.

1.3 Organization

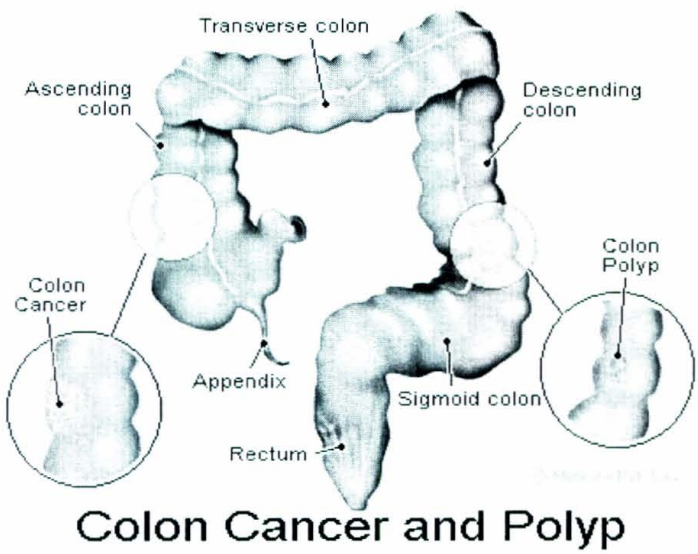
This thesis is divided into six chapters. Chapter 1 is an overall introduction to this study. Chapter 2 reviews the epidemiologic description and associated risk factors of CRC. Chapter 3 presents the research methods employed in this study. Chapters 4 and 5 are both results sections, which are written in a manuscript format, including its own introduction, methods, results, and discussion. Some repetition of methods was unavoidable. Chapter 6 summaries the key findings and discusses implications of the study results.

Chapter 2 Literature Review

2.1 Colorectal Cancer

Colorectal cancer (CRC) encompasses malignancies originating from the epithelial cells of gastrointestinal tract, which includes the colon, rectum and appendix [44]. The colon is the first four to five feet of the large intestine, which consists of the cecum, the ascending colon, the transverse colon, the descending colon, and the sigmoid colon (Figure 2.1). The main function of the colon is to remove water and nutrients from the food mass and convert the rest into waste [45]. The rectum is made up of the last several inches of the digestive tract [45]. Its major function is to store waste material prior to excretion.

Figure 2.1: The colon and rectum polyp and cancer



Source: www.encognitive.com/node/10376

CRC usually begins as a noncancerous polyp which may eventually become a cancerous growth. This process may vary from several years to decades. Initiation and progression through the adenoma-carcinoma sequence is linked with accumulated defects in tumor suppressor genes, oncogenes, and DNA repair genes [46]. The tumor genesis may be started by external agents and/or inherited genetic factors [47].

2.2 Epidemiology of Colorectal Caner

2.21 Worldwide Burden

CRC is one of the most common cause of cancer deaths each year in men (663 000 cases, 10.0% of the total) and the second in women (571 000 cases, 9.4% of the total) worldwide [48]. The majority (60%) of the cases occur in developed regions, which includes Australia/New Zealand and Western Europe [49]. On the other hand the fewest cases occur in Africa (except Southern Africa) and South-Central Asia [49]. Men usually have higher incidence rates than women (overall sex ratio 1.4:1) [49]. The worldwide estimated deaths from colorectal cancer are about 608 000 deaths per year; Central and Eastern Europe experience the highest mortality rates in both sexes estimated as 20.1 per 100,000 for males and 12.2 per 100,000 for females. Middle Africa experiences the lowest male and female mortality rates of 3.5 and 2.7 respectively [49].

2.22 Canadian Incidence and Mortality

In Canada, 22,500 diagnoses and 9,100 deaths were expected from colorectal cancer in 2010 [11]. CRC is the fourth most common malignancy and the second leading cause of death from cancer in men and women combined [11]. In 2010, the age-standardized incidence rate of CRC was 62 per 100,000 among men and 41 per 100,000 among women, and the age-standardized mortality rate was 25 per 100,000 men and 16 per 100,000 women [11]. More than 50 percent of newly diagnosed colorectal cancer cases will occur among people aged 70 years or older [11]. Although the age-standardized rates are higher in men, the number of prevalent cases and deaths is approximately equal between the sexes because of the tendency of women to live longer than men.

The 2010 Canadian Cancer Statistics reported the fluctuation of CRC incidence: the

incidence rose between 1980 and 1985; next, the incidence declined to the mid- 1990s (more strongly in females than in males), then rose through 2000, only to decline significantly thereafter [11]. Recent declines in mortality rates in both sexes may be due to high screening rates, improved controls and/or treatments.

Interprovincial variations for colorectal incidence and mortality rates are obvious [11]. Newfoundland and Labrador typically has the highest rates of colorectal cancer in Canada at a rate of 88 per 100,000 for men and 52 per 100,000 for women in 2010. Ontario ranks in the middle among Canadian provinces at a rate of 59 per 100,000 for men and 40 per 100,000 for women in 2010. British Columbia has the lowest incidence with a rate of 54 per 100,000 for men and 37 per 100,000 for women. The high colorectal incidence in Newfoundland and Labrador may be partly explained by a high prevalence of families with a predisposition to hereditary colon cancer [50]. However, environmental factors are also an important component to the CRC risk.

2.3 Risk Factors Associated with CRC

The exact causes of colorectal cancer are unknown [45]. While family history is a strong risk factor for CRC, inherited familial CRC is responsible for 10%-15% of all CRC cases [51-53] and the majority of CRC cases are a result of gene-environment interactions [52, 54, 55]. Lifestyle and dietary factors play an important role. About 75 to 85 percent of CRC are sporadic, suggesting that modifiable factors are of public health importance and etiology. Important modifiable risk factors for CRC include tobacco use, unhealthy diet, physical inactivity and the consumption of alcohol [47].

2.3.1 Hereditary Factors

Those with a family history of CRC or adenomatous polyps in any first-degree relative younger than age 60, or in two or more first-degree relatives at any age are considered at increased risk for the disease. Among familial cases, approximately 5%-10% of CRC are a consequence of hereditary genetic mutations, which mainly consist of familial adenomatous polyposis (FAP), and hereditary non-polyposis CRC (HNPCC) [56, 57].

Patients who have FAP typically develop hundreds of polyps in their colon and rectum during the ages of 5 to 40 years. FAP is commonly caused by mutations of the adenomatous polyposis coli gene, which result in inoperative tumor cell growth and finally leads to the growth of hundreds of polyps in the colon and rectum. Over time, gene mutations in the cells of the polyps cause the polyps to become cancerous [58]. FAP accounts for less than 1% of all CRC patients [59].

HNPCC accounts for 1% - 6% of all CRCs [60-62]. This syndrome also develops when people are relatively young. Patients with HNPCC have fewer polyps, unlike hundreds of polyps as is seen in patients with FAP. HNPCC syndrome is characterized by early onset of CRC with microsatellite instability. Microsatellite instability of the cancer tumor is a molecular marker for DNA mismatch repair deficiency. Mutations in mismatch repair genes are detected among 85% of HNPCC patients [58].

2.3.2 Environmental Factors

Existing studies show that immigrants rapidly acquire the incidence rates of their host country, suggesting that environmental factors play a crucial role in CRC development

[63-65]. As mentioned in Chapter 1, the WCRF and AICR second expert report classified risk factors into four major groups according to the strength of the evidence. Evidence linking physical activity to CRC is convincing as well as red meat, processed meat, excessive alcohol drinking (above 30g/day), body and abdominal fatness, and adult attained height (the difference between current weight and weight at their age of 20s); intakes of dietary fibre, garlic, milk and calcium probably reduce CRC risk; intakes of non-starchy vegetables, fruits, folate, selenium, fish and vitamin D have limited suggestive evidence of declining CRC risk; intakes of iron, cheese, food containing animal fat, and sugars are limited but inconclusive evidence of raising CRC risk. This expert report also suggested CRC is mostly preventable by appropriate diets and associated factors.

2.3.2.1 Socio-economic Status (SES)

There are great geographic variations in incidence rates. Rates have been shown to be higher in the western countries and lower in developing countries. Countries with high incomes have been shown to have higher colorectal cancer incidence rates than those with lower incomes [66]. This may be partly explained by the fact that residents in the developed countries have a "westernized" dietary pattern with less physical activity associated with both occupation and transportation due to industrialisation. Findings from several studies suggested that the risk of developing CRC increased with a higher education level and social class [67, 68]. On the other hand, low SES predisposes people to certain risk factors (e.g. poor dietary intake and obesity), which in turn may interact with genetic factors and lead to the occurrence of colorectal cancer. There are different social class correlates for colon and rectal cancer [67]. The two sites should not be combined in studies considering lifestyle factors in the aetiology of these neoplasms [67].

2.3.2.2 Dietary Factors

Dietary factors have been regarded as strongly associated with the incidence of CRC [53, 69], particularly when an unhealthy diet is intermingled with obesity, weight gain, physical inactivity, smoking or excessive alcohol consumption [18, 34, 70-74]. One study has indicated that about 70% of CRC can be prevented by changes in diet and lifestyle [73], but estimates vary widely [53]. Although epidemiologic studies and/or clinical trials have attempted to examine the associations among specific foods, nutrients and CRC, the results produced are inconsistent and unconvincing.

The 'Western' diet, known to be high in animal fat, red and processed meats but low in fruit, vegetable and fibre content, has been linked to an increased risk of CRC. This type of diet is common for people who live in Japan, North America, Northwestern Europe and Australia.

2.3.2.2.1 Total Energy

The 2007 World Cancer Research Fund and the American Institute for Cancer Research expert report concluded that total energy has no simple relation with CRC risk. Data are inconsistent for carbohydrates, proteins and cholesterol [75]. Several studies have suggested that total energy intake is positively associated with CRC risk [76-78]. High energy intakes could cause a glycemic overload, a compensatory increase of serum insulin, and related insulin growth factor-1 (IGF-1), leading to an increased cell proliferation, reduced apoptosis, and thereby increase the risk of tumorigenesis [79-82]. This may help to explain why patients with non-insulin dependent diabetes have increased CRC risk [81, 83-86]. In addition, the effects of hyperinsulinemia and type 2 diabetes have been shown to be associated with increased risk of proximal rather than distal colon cancer [84, 87]. Patients with type 2 diabetes are predisposed to lower survival rates and higher recurrence rates. Another possible

explanation could be that people with CRC and type 2 diabetes share similar unhealthy lifestyles [84].

2.3.2.2.2 Fruit, Vegetables and Fibre

Ever since Burkitt proposed that a lower CRC mortality in blacks compared to the whites was attributable to dietary fibre intake, the risk of colorectal cancer in relationship to fruit, vegetables and fibre has been examined by hundreds of epidemiologic studies [56]. The 1997 WCRF/AICR expert panel reviewed 21 case-control and four cohort case-control studies and concluded that vegetable consumption convincingly reduces the risk of colorectal cancer but the evidence supporting fruit consumption was limited [88]. Subsequently, the 2003 IARC evaluated 27 case-control and 13 cohort studies and suggested that higher intakes of vegetable probably declines the CRC risk and higher intakes of fruits possibly reduces risk [49]. The latest 2007 WCRF/AICR expert report indicated that fibre is probably associated with CRC risk reduction and that non-starchy vegetables and fruits have limited suggestive evidence of declining risk [56].

Overall, case-control studies showed that fibre provided approximately a 40%-50% of reduction in the risk for colon cancer while prospective cohort studies indicated a weak association between dietary fibre intake and colon cancer [32]. One meta-analysis showed that an increase of 10 g fibre per day was responsible for a 10% reduction in CRC risk (RR: 0.90 and 95% CI: 0.84-0.97) [56]. With this being said, some studies suggest that the effects of fruit, vegetables and fibre may only be evident for a person who has low baseline intake levels [32].

Many fruits, vegetables and grains are rich in fibre. Fruits and vegetables are sources of

dietary fibre, carotenoids, folate, selenium, glucosinolates, vitamins and minerals [56]. The precise mechanisms explaining the beneficial role of fibre, fruits and vegetables are not clearly understood. The protective effect of fibre may be linked with the fact that fibre dilutes fecal contents, decreases transit time and increases stool weight [32, 89], which helps to reduce the time of exposure to carcinogens or tumor promoters in the intestinal lumen [90]. The beneficial effect of fruits and vegetables may be attributed to the combined influences of constituents on several carcinogenesis pathways. Antioxidants contained in the fruits and vegetables could protect against oxidation damage through trapping free radicals and reactive oxygen molecules [32, 56]. Short-chain fatty acids produced in the fermentation process might induce apoptosis; therefore also possibly contributing to their beneficial role [32].

2.3.2.2.3 Meat and Fat

For the purpose of this thesis, the term "*red meat*" refers to beef, pork, lamb and goat from domesticated animals and "*processed meat*" refers to meats preserved by smoking, curing, or salting or by the addition of preservatives [56]. Red and processed meat has been postulated to increase CRC risk through several mechanisms such as the production of heterocyclic amines and polycyclic aromatic hydrocarbons with high temperature cooking method such as frying, grilling, and barbecuing [91, 92]; increased exposure to mutagenic nitrites, nitrates, N-nitroso compounds and salts [93]; stimulation of endogenous insulin which can cause cell proliferation [32]; or increased iron intake, which is considered an emerging carcinogen that may increase the formation of oxygen species and consequently lead to DNA and chromosome damage [27, 94].

The expert panel conducted a meta-analysis of 16 cohort studies which indicated that a daily increase in the consumption of 50 gram of red meat was associated with a 15% increase

in CRC risk [56]. The panel also showed that a daily 50 gram increase in the consumption of processed meat of was linked with a 21% increase in CRC risk [56]. Therefore, the panel concluded that the evidence linking red and processed meat consumption with risk of CRC is convincing.

Dietary meat alternatives including fish and poultry have been associated with deceased CRC risk in most, but not all studies [33, 35, 56, 95, 96]. The mechanism is not clear. It has been proposed that n-3 polyunsaturated fatty acids in fish protect against CRC by reducing inflammation and regulating DNA methylation [97-102]. Animal trials have indicated that fish oil supplements decrease the number of colon tumors [103]. Long-chain n-3 PUFAs in fish oils can inhibit tumor cell proliferation by modifying signaling pathways [104, 105]. The evidence to support that fish and poultry intakes are associated with a reduction of CRC risk is limited [56]. The EPIC study suggested that the consumption of red and processed meat increases colorectal cancer risk while the intake of fish decreases it [98].

Meat is a major source of dietary fat, especially of saturated fat [32]. Some studies have shown that an increased risk of CRC is associated with an increased intake of total saturated fat while intakes of monounsaturated and polyunsaturated fats have been found to be associated with a reduced risk [106, 107]. A diet high in animal fats reflects higher consumption of meats and a lower consumption of vegetables and fruits. Such energy-dense diets have been directly linked with increased CRC risk or mediated through obesity. However, the women's health study [108] and a prospective cohort study of male health professionals [79] showed that diets low in fat had no effect on CRC risk reduction. There is limited evidence suggesting that dietary animal fat is associated with risk of CRC.

2.3.2.2.4 Minerals and Vitamins

Calcium, selenium, vitamin D, vitamin B complexes, beta carotene and antioxidants have anti-carcinogenic effects and thus decrease CRC risk [109-111], whereas iron has been shown to increases the risk [112]. One of the most well studied minerals in CRC prevention is calcium, which is mainly found in dairy products and supplements. Calcium is known to bind secondary bile acids and ionized fatty acids in the colon lumen to form insoluble calcium soaps, preventing bile acids and fatty acids from damaging the mucosa of the intestinal lumen by inhibiting their proliferative effects [113]. Calcium may also function by reducing cell proliferation, stimulating differentiation, inducing apoptosis, and regulating the cell-cycle of normal and tumor colorectal cells [114-117]. The roles of dietary calcium and vitamin D are highly correlated because both participate in cell growth restraining, differentiation and apoptosis in intestinal cells and vitamin D regulates the absorption of calcium. Some of the effects of dairy intake on CRC risk reduction is mediated through calcium, although other bioactive constituents may have potential effects as well.

The vitamin B complexes are linked with carcinogenesis through DNA synthesis, repair and methylation [111, 118, 119]. High intake of folate and its cofactors (vitamins B6 and B12) are associated with a 30% reduction in CRC risk [111, 120-122]. One meta-analysis has suggested that folate found in naturally in foods rather than folate in the form of supplements has a beneficial effect. This might suggest that folate combined with other constituents, or in its certain active form, is truly effective in CRC prevention [32, 123].

Antioxidants, including carotene; vitamins A, C, and E; and selenium may protect against CRC through their antioxidant or anti-inflammatory characteristics [122]. Findings of observational studies, meta-analyses and placebo trials are not consistent as they pertain to

the protective effect of anti-oxidants, either as single agents or in combination with other antioxidants [124-127].

2.3.2.2.5 Dietary Patterns

Most available studies in nutritional epidemiology have investigated the effect of individual foods and nutrients [32]. Although diet and colon cancer relationships have been studied extensively, the impact of many dietary factors on colon carcinogenesis remains unresolved [27, 79, 90, 128-138]. Foods are often consumed together and similar nutrients can come from different foods; therefore, examination of the specific effect of each food is likely to be confounded by other foods consumed throughout the diet [139, 140] . Consequently, an increasing number of studies in the past decade have examined the associations between dietary patterns and CRC [36, 71, 141-148]. A number of food patterns have been identified [56], such as Asian, plant-based, Mediterranean and westernized diets. Nevertheless, overall the evidence is meager and heterogeneity of dividing food groups exists.

2.3.2.3 Physical Activity

Physical activity includes activities that are associated with occupation (at work), home, recreation (leisure) and transportation (such as walking, riding, and cycling). Engaging in physical activity has long been considered an effective strategy for CRC prevention [12]. Undertaking 150 minutes of moderate physical activity each week can reduce the risk of breast and colon cancers. In industrialized countries with high incomes, sedentary life is normal with occupational and household physical activities being dramatically reduced in recent decades- 31% of the world's population is not physically active [56, 149].

Systematic reviews have found that increased physical activity is a substantial protective factor against colon or colorectal cancer [13-16]. Numerous prospective [17-20] and case-control [21, 22] studies have found statistically significant associations between physical activity and colorectal cancer, particularly in men. However, a few studies have not found significant associations [23-25]. The beneficial role of physical activity in prevention of colon and/or rectal cancer varied in sub-sites and sex [17, 21, 25, 26, 150-153]. The WCRF and AICR [154] summarized 24 cohort studies and found that all but two of these studies have reported decreased risk. Higher levels of recreational activity were found to help protect against colon cancer in both men and women with a significant inverse trend being reported in six of 24 cohort studies. Physical activity was not associated with decreased risk of cancer of the rectum.

A few previous studies have indicated that intense physical activities have a greater CRC risk reduction. Researchers have demonstrated that a lack of lifetime vigorous leisure-time activity was associated with increased risk of colon cancer for both men and women [155].

2.3.2.4 Smoking

Tobacco use is the single most important risk factor for cancer [47]. This may be explained by the carcinogens that are released through smoking [32, 156]. Higher smoking prevalence in Atlantic Canada is associated with higher rates of lung cancer in this region [11]. Tobacco use has been associated with colorectal adenoma and cancer; however, the association has been observed to be stronger for rectal cancer [72, 157] and proximal colon cancer relative to the distal colon cancer [158, 159]. Higher levels of daily cigarette consumption and longer duration of smoking (pack-years), often associated with an earlier age of initiation, were associated with higher CRC risk. This suggests the presence of a

strong dose-response relationship between smoking and increasing CRC risk [72]. Past smokers appear to have a higher incidence of CRC as compared to current smokers; however, this may be confounded by the early damage caused by early initiation of smoking [32].

2.3.2.5 Alcohol Consumption

Most studies, but not all, indicate that alcohol consumption increases CRC risk. Meta-analysis of cohort data suggested that a 10 g daily ethanol intakes increase CRC risk by 9% [56]. Alcohol may mediate prostaglandin production, increase lipid peroxidation and oxidative species, and consequently result in increased carcinogenesis through the mechanisms of abnormal DNA methylation and/or activation of cytochrome p 450 enzymes [56, 160, 161]. Alcohol is predicted to have the function of acting as a solvent for carcinogenic molecules in mucosal cells [56].

2.3.2.6 Obesity and Abdominal Fatness

Obesity (Body Mass Index $\geq 30 kg/m^2$) and abdominal fatness (measured by waist circumference > 102cm in men and >88 cm in women or waist to hip ratio of >0.9 for men and >0.85 for women) are convincingly associated with CRC risk [56]. The association was stronger for men compared to women and for the colon relative to rectum [32, 162]. The 2007 WCRF/AICR expert report shows a 15% increased CRC risk per 5 kg/m^2 BMI increase and 5% increased risk per inch of waist circumference [56]. Several biological mechanisms have been proposed to understand the associations. Obesity results in insulin resistance, which leads to cancer pathogenesis mediated by the mitogenic property of insulin and hyperinsulinemia. Insulin stimulates increased free insulin growth factors which promote carcinogenesis [163-165]. Obesity and abdominal fatness also have relationship with

oestrogens, leptin, and chronic inflammation, which are all associated with increased CRC risk [166-170].

2.3.2.7 Medications

Clinical trials, cohort and case-control studies have shown that the use of aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) was associated with decreased CRC risks [171-173]. The anti-cancer effects of NSAIDs and aspirin may be exerted through the inhibition of cyclooxygenase and lipoxygenase enzymes [173], inhibition nuclear factor-Kb [174], induction of apoptosis by activation of kinase [175], and polyamines catabolism [176]. All of these factors play key roles in the function of various cellular metabolisms.

Chapter 3 Research Methods

3.1 Data Sources

The U.S. National Cancer Institute established the Ontario Familial Colorectal Cancer Registry (OFCCR) as one of six international sites in the consortium of Colon Cancer Familial Registries (CCFR) in 1997 [177, 178]. The *CIHR Team in Colorectal Cancer* (CTCC) aimed to improve the knowledge of the determinants, impact, and control of colorectal cancer as a result this team established the Newfoundland Familial Colorectal Cancer Registry (NFCCR), which was modeled on OFCCR (details on the project can be found at: http://www.mshri.on.ca/colorectalcancer/). The study addressed by this thesis used the database of a population-based Newfoundland and Ontario Colorectal Cancer Study (NOCS). Ethics approval was obtained from the Research Ethics board of Memorial University.

The original data-base cleaning involved checking and verifying missing data, conducting range and value checks, and conducting logic and reverse logic checks [31]. The data base cleaning process involved the conversion of cell values, variable names, variable types, variable lengths, and column widths in the original data, which has all been done by previous OFCCR and NFCCR research team members. However, for this thesis study, additional variables required for analysis were derived and variable names were adapted for specific software requirements.

3.2 Study Design

Both Ontario and NL colorectal cancer studies used a population-based case-control study design to collect necessary information. Case control studies can identify risk factors of disease, especially for rare diseases, by comparing the odds of given risk factors between

cases and controls. The incidence rate of CRC in Canada meets this criterion for a rare disease; consequently, a case-control study design makes sense for the study. All eligible cases identified through the Ontario Cancer Registry and the Newfoundland Cancer Treatment and Research Foundation were invited to participate in this interdisciplinary CRC study. Controls were five-year age group and sex matched to cases. The detailed description of inclusion criteria would be outlined in the next section: study population.

3.3 Study Population

3.3.1 Cases

The Ontario Cancer Registry and the Newfoundland Cancer Treatment and Research Foundation were used to identify newly diagnosed cases of colon or rectal cancer; and cases were recruited into the OFCCR and NFCCR. Pathologists in the study confirmed the pathology reports of cases. Inclusion criteria for cases [179]:

1) Incident primary invasive colon or rectal cancer [pathology confirmed International Classification of Diseases 9th revision codes: 153.0-153.9, 154.1-154.3 and 154.8 (ON & NL); or ICD-10 codes: 18.0-18.7, 19.9, 20.9 (NL only)];
2) Diagnosed between July 1997 and June 2000 (phase one) or January 2003 and April 2006 (phase two) in ON. Diagnosed between January 1999 and December 2003 in NL;
3) Diagnosed at ages of 20 to 74 years old (phase one) or ages of 20 to 50 years (phase two) in Ontario; and
4) Residents of ON and NL at the time of diagnosis.

The pathologists of this study identified eligible cases by viewing pathology reports generated by the Ontario Cancer Registry and the Newfoundland Cancer Treatment and

Research Foundation. Initial contact was made through the surgeon/physician identified on the pathology report. A letter was sent to the physician that described the study and requested permission to contact the patient. Once physician consent was obtained, individuals were then contacted by researchers to inform them of the study. Participants who indicated their willingness to participate the study were sent, in sequence, a written consent form, Family History Questionnaire (FHQ). Then, cases were categorized into high, intermediate, and low risk of CRC (based mostly on family history). Subsequently, 100% of high and intermediate, and only 25% of the sporadic cases were invited to fill in Personal History Questionnaire (PHQ), Food Frequency Questionnaire (FFQ). In NL only, the original study packet also contained a blood requisition form.

If a participant did not return finished questionnaires within three weeks, and a follow-up telephone call was made to ensure the study package had been received. In certain circumstances, a telephone interview or assistance was offered, especially when illiteracy or physical disability was a concern. Subjects were provided with a toll-free telephone number as a way to contact study staff if they had questions regarding any of the items on questionnaire or procedures required for the study. Multiple telephone follow-ups were conducted if eligible participants did not respond to survey questionnaires. If a subject made any indication of not wanting to participate in the study, the interviewer attempted to determine and record the reason. No further contact was made with these subjects. Family history questionnaires were used to classify families as high, intermediate or low risk for genetic counseling. In NL where blood samples were collected, the samples were sent directly from the laboratory closest to the participant to a central laboratory for investigation of genetic markers.

3.3.2 Controls

Controls recruited by the OFCCR and NFCCR were comprised of a random sample of residents aged 20-74 years in each province. Within a frequency matched case-control study, controls were 5-year age group and sex matched with the colorectal cancer cases. In Ontario, controls were identified through a list of residential phone numbers provided by Bell Canada during 1999 and 2000. Info-direct, a service from Bell Canada, provided information pertaining to potential control subjects, which included their names, telephone numbers, and addresses. Households were randomly selected from this list and telephoned to obtain a census of household members (age and sex) as a method to identify eligible persons. One eligible person within each household was randomly selected and invited to participate in the OFCCR. To increase the sample size and match the case to control ratio was 1:2; therefore, additional controls were identified from population-based assessment rolls (owners and occupants) provided by the provincial government during 2001 and 2002. The detailed description of controls selection can be found within other publications of this interdisciplinary CRC study [180, 181].

In NL, controls were identified through random digit dialing [182]. Initially, a set of 192,000 possible residential telephone numbers were generated and randomly arranged. A research assistant with prior experience in telephone surveying made the initial contacts by dialing those numbers in a sequential order until the desired number of controls was reached. A screening interview was conducted among potential control subjects to identify if there was an eligible household member based on their sex and age and whether that person was willing to receive a mailed family history questionnaire.

In both provinces, once verbal consent for participation was obtained through telephone

contact, a survey package was forwarded to each potential participant. The package included an information pamphlet with general information concerning the study, a consent form, Personal History Questionnaire (PHQ), Food Frequency Questionnaire (FFQ), Family History Questionnaire (FHQ), as well as a self-addressed stamped envelope. If a participant did not return complete questionnaires within three weeks, a follow-up telephone call was made to ensure that the study package had been received. A telephone interview or assistance was offered when illiteracy or physical disability was a concern.

3.4 Response Rates

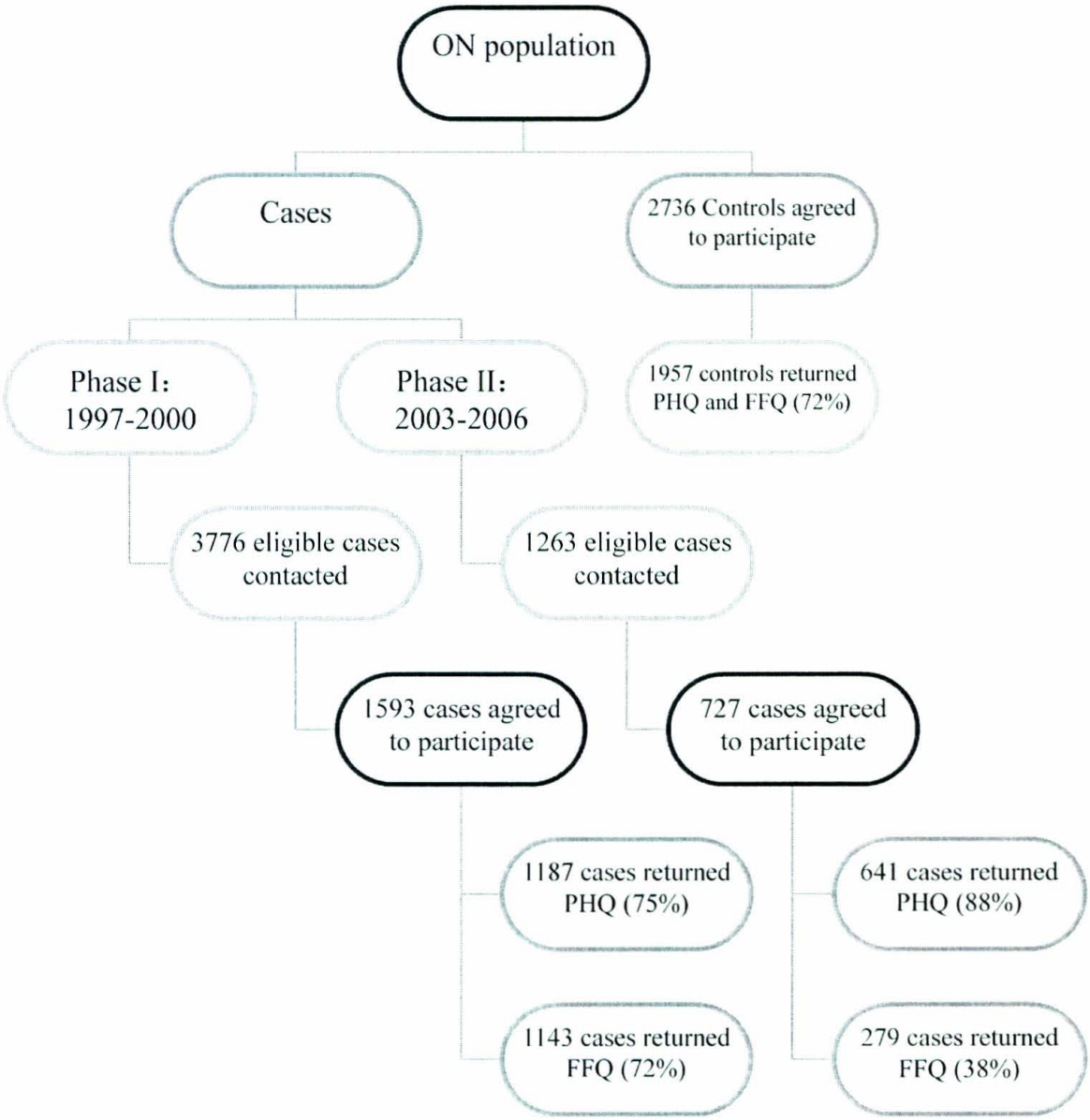
3.4.1 Response Rates in Ontario

During phase-one of the OFCCR (1997-2000), a total of 3776 eligible CRC cases were identified in Ontario. After the initial contact with the physicians and eligible CRC cases, 1593 were willing and able to participate in the registry out of which 1187 cases (75%) completed the PHQ and 1143 cases (72%) completed the FFQ.

Phase two of the OFCCR was initiated in January 2003 and scheduled to continue to the end of 2006. Consequently, phase two data which were available up to April 2006 were used in this thesis. During this period, among the 1263 eligible patients that were contacted, 727 of which agreed to participate in the registry. PHQs were returned by 641 (88%) cases and FFQ were returned by 279 (38%).

Population controls in Ontario were contacted via telephone calls. A total of 2736 control subjects from Ontario agreed to participate in the study, of which 1957 (72%) completed all three questionnaires (FHQ, PHQ, and FFQ).

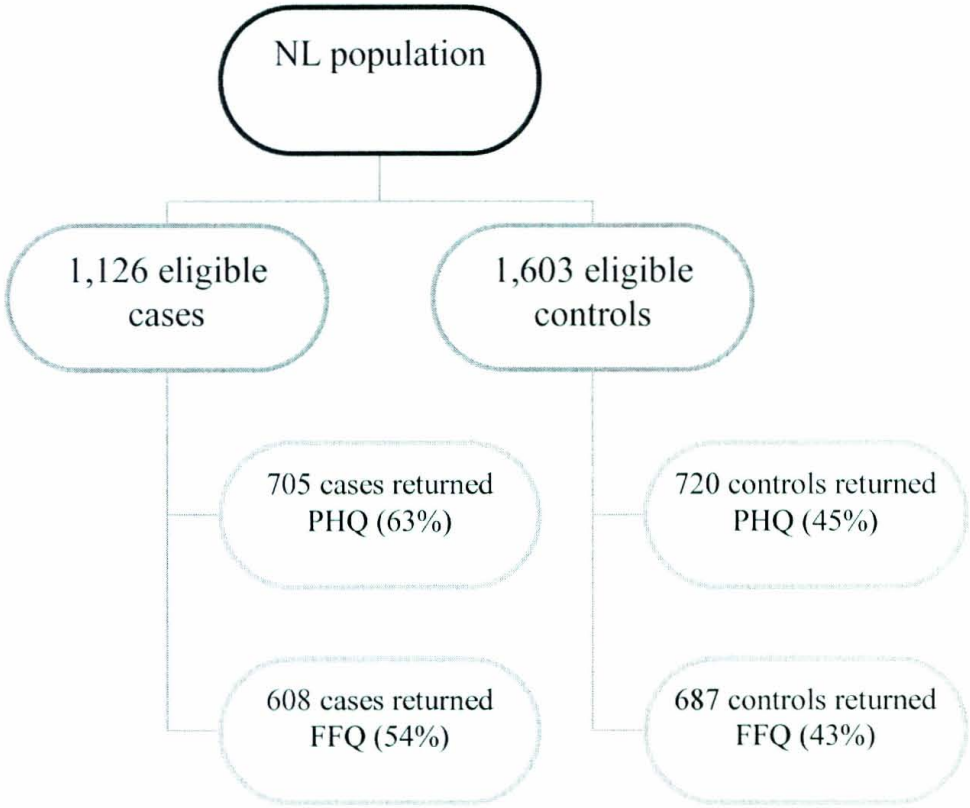
Figure 3.1. ON population sample size and response rates (adapted from Sun [183])



3.4.2 Response Rates in Newfoundland and Labrador

In total, among 1126 eligible NL CRC cases, 705 (63%) participated and returned the PHQ, and 608 (54%) returned the FFQ. Population controls in Newfoundland and Labrador were contacted through random digit dialing. The total number of telephone calls made was not recorded. In July 2005, 1,603 controls had agreed to participate in the study in some form. 720 controls (45%) returned the PHQ and 687 controls (43%) returned the FFQ.

Figure 3.2. NL population sample size and response rates (adapted from Sun [183])



3.5 Data Measurement

All participants in the interdisciplinary CRC study were asked to complete self-administered mailed epidemiologic questionnaires, which include the Personal History Questionnaire (PHQ), the Food Frequency Questionnaire (FFQ), and the Family History Questionnaire (FHQ). OFCCR and NFCCR used the same PHQ and FHQ but the FFQ between ON and NL had some are differences.

3.5.1 Personal History Questionnaire (PHQ)

The PHQ was designed to investigate 74 items of information pertaining to participants, addressing detailed identifying information: demographic characteristics (age, sex and marital status), bowel screening history (hemoccult test, sigmoidoscopy, colonoscopy, and endoscopy

test) and health history (diabetes, high cholesterol, high triglyceride, etc), medication use (non-steroidal anti-inflammatory drugs, bulk-forming laxatives, other laxatives), physical activity (specific activities such as walking, jogging, and running during their 20's, 30-40's, and 50's), alcohol consumption (beer, wine, sake, liqueurs during their 20's, 30-40's, and 50's), tobacco use, socio-demographic factors (education, income and residence) and anthropometric measures (height, body mass index). Among female participants, additional questions addressing menstruation; pregnancy; ages at menarche; first birth; and menopause; parity; hysterectomy; oophorectomy; menopausal status; and reason for menopause were surveyed. This questionnaire can be found in Appendix 1.

3.5.2 Food Frequency Questionnaire (FFQ)

The FFQ administered in the ON population was originally developed for the Hawaiian and Californian populations by the Epidemiology Program of the Cancer Research Center of Hawaii, which has been previously described and validated against 24-h recalls of a multi-ethnic Hawaiian/Southern Californian population[184, 185]. See Appendix 2. The FFQ surveyed regular food consumption, and cooking methods of 170 common foods about one years before their diagnosis for cases or their interview for controls. Participants were asked to choose the portion size of their usual serving for each listed food item from 'Regular', 'Small' or 'Large'. The frequency of food consumption was assessed using 8 options (never or hardly ever, once a month, 2-3 times a month, once a week, 2-3 times a week, 4-6 times a week, once a day, 2 or more times a day). Subjects were also asked to provide information on their use of multi- or single vitamin and/or mineral supplements, including the usual brand, dosage, and duration of supplement intake.

FFQ administered in NL was developed from the FFQ used in Ontario to adapt to the

unique food consumption pattern if the province. Participants were asked to estimate the frequency and portion size of 169 food items one year prior to their diagnosis or participation in this study. For each food item, subjects were asked to estimate the frequency of food consumption (daily, weekly, monthly and never scales) and their usual portion size (average, smaller or larger) about one year their diagnosis for cases or their interview for controls. The information on vitamins and other dietary supplements was also collected.

3.5.3 Family History Questionnaire (FHQ)

The FHQ helped to collect information of the diagnosed type of cancer or tumour history of participants. The same questions were used to survey the participant's mother, father, children, brothers and sisters, mother's brothers and sisters (NL only), father's brothers and sisters (NL only) and other relatives who had cancer.

3.5.4 Study Outcomes and Exposure Variables

For both cases and controls, CRC was the outcome in this thesis. For the first objective of this thesis, the main study exposure was recreational physical activity. It was measured by self-reported data from the PHQ on current and past activities of participants: the frequency and duration of walking, jogging, running, bicycling, swimming, tennis, squash/racquetball, calisthenics, aerobics, vigorous dance, football, soccer/rugby, basketball and subjects' self-reported participation in other sports when a participant was between the ages of 20-30, 30-50, and 50 or older. The questions regarding physical activity were "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. Walking-yes or no; 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?" The same questions were asked of jogging, running, bicycling, swimming and so on addressing three periods in total (20-30s, 30-50s, and 50s plus). Participants were asked to specify the frequency and duration of activities not included on the questionnaire but participants did consider to be recreational exercise.

The derived time taking frequency and duration into consideration, that the participant spent on each exercise after they reached the age of 20 was multiplied by its specific metabolic equivalents score (METs) to yield a MET-hour score [186, 187]. Average weekly MET hours for walking, non-walking exercise and total recreational physical activity were calculated. After calculation, walking, non-walking exercise and total recreational physical activity were further divided into quintiles according to percentage distribution of controls ($<$Q20, $<$Q40, $<$Q60, $<$Q80, $\geq$Q80).

For the second objective of this thesis, the complex inter-relationships among socioeconomic status (SES), lifestyles, diet, and health involve a wide range of exposures. The core variables were divided into several aspects. Putative covariates for the main exposure variables included: 1) demographic factors: age (18-39, 40-49, 50-59, 60-69,70+), sex (male, female), marital status (single or never married, currently married or living as married, separated, divorced or widowed), 2) socio-economic status: educational levels, household income(0-$11,999, $12,000-$29,999, $30,000-$49,999, $50,000 plus), residence (rural, urban); 3) medical history: any screening procedure which included hemoccult test, sigmoidoscopy test and colonoscopy, indicated as dichotomous (yes/no); self-reported health conditions were coded as "yes/no": polyps, familial adenomatous polyposis, Crohn's, colitis, diabetes, high triglycerides/cholesterol; use of medications and supplements: non-steroidal anti-inflammatory drugs, bulk forming laxatives, non-bulk forming laxatives; 4) dietary

patterns measured by food groups (units: gram or servings/day); 5) average weekly MET hours of physical activity level at ages of 20-29, 30-49, 50+, and lifetime; 6) alcohol consumption: average weekly drinks at ages of 20-29, 30-49, 50+, and lifetime; 7) smoking: cigarette smoking status (current, former and never) and pack-years; 8) BMI categorized by World Health Organization (WHO) criteria: underweight (<18.5 kg/m^2); normal weight (18.5-24.9 kg/m^2); overweight (25-29.9 kg/m^2); and obese (≥30 kg/m^2). Two BMI indices were used for this analysis: first, recent-BMI was calculated from body weight during the reference period (one year prior to diagnosis for cases or one year prior to participation for controls); second, BMI at about the age of 20 was estimated from their self-reported body weight at the age of 20. Other primary exposures of interest included adult weight gain, which was derived by getting the difference between their weight (kg) at 20 years of age and recent weight (kg), and adulthood height (m). Among women only, additional potential confounders included: ages at menarche, first birth, and menopause; parity; hysterectomy; oophorectomy; menopausal status; and reason for menopause. The main study variables were also assessed for confounding influence on each other.

3.6 Data Analysis

To analyze the data collected for the first objective, SAS statistical software (version 9.1 SAS Institute, Cary, NC, USA) was used. M-PLUS 5.0 software (Muthen & Muthen) were used to perform statistical analyses for the second objective of this thesis.

3.6.1 Descriptive Analysis

Uni-variate analysis was done to examine distributions and detect outliers. The exposure variables of cases and controls were compared by *t* tests for continuous variables, and

chi-square test for categorical variables. All tests of statistical inference employed a two-sided alpha level of 0.05.

3.6.2 Multivariable Regressions

To address the first objective of this thesis, sex specific age-adjusted and multivariate adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated using unconditional logistic regression to assess the associations between physical activity and CRC risk. Tests for linear trend were done by modeling the median value of each quintile of physical activity measured by metabolic equivalent (MET) hours per week into the logistic regression model.

3.6.3 Structural Equation Modelling

The direct and indirect effects for various risk factors on colorectal cancer were tested using structural equation modeling (SEM). SEM is a multivariate technique combining aspects of multiple regressions examining dependent relationships and factor analysis representing non-directly measurable concept or latent variables measured through multiple indicators to simultaneously estimate a series of interrelated dependence relationships [188, 189].

SEM analysis is primarily confirmatory in nature and basically consists of two primary components, the measurement model and the structural equation model [188, 189]. The measurement model involves using factor analysis to develop an acceptable model, which reduces observed measured variables to a smaller number of latent variables factors and to ensure that the indicator variables loaded significantly on underlying latent factors. The

structural equation model defines the relationships among these observed variables, latent factors and covariates.

Traditional techniques, such as regression and path analysis, analyze only measured variables; however, SEM takes into account of measurement error and could deal with latent variables which are not directly measurable. Factors are signified with circles and the observed variables are represented with rectangles. Using measured variables as indicators of latent factors rather than simply taking the sum or average of the measured items as a scale allows for estimation and removal of the measurement error associated with observed variables [188].

Food groups dietary patterns and lifestyles were represented by latent variables. However, due to the complexity of the dietary and life styles factors, several approaches (single latent, multiple latent, and manifest variables) were explored and compared. This was guided by exploratory factor analysis, and our understanding of the associations of interest. Genetic factors should be considered in building models so this study took the family history score of CRC (previously derived) as a continuous variable into consideration. We felt this simplification was necessary in order not to lose sight of the main objective. Other factors, such as age, gender, and comorbidities have also been considered. However, since other variables are not our primary interest, this study only considered some main common candidate risk factors of CRC as potential confounding factors. The conceptual models would also be revised and compared with a number of competing models.

Model fit indices were evaluated based on the following: Comparative Fit Index (CFI), the Tucker Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA),

Weighted Root Mean Square Residual (WRMR), and Standardized Root Mean Square Residual (SRMR).

Chapter 4 Project 1:Walking, Non-walking Exercise and Colorectal Cancer - a large population based case-control study in Canada

4.1 Abstract

Background:

Higher levels of physical activity have been consistently associated with a lower risk of colorectal cancer (CRC) in previous studies. Nevertheless, the specific mode, intensity, frequency, and duration of physical activity required for colorectal cancer prevention are not well known and remain controversial. This study examined the associations among walking, non-walking exercise, total recreational physical activity and colorectal cancer risk.

Methods:

This study used data collected from an existing population based case-control study in Ontario and Newfoundland and Labrador, which collected participant's personal history, life style and dietary information using a Personal History Questionnaire (PHQ), Food Frequency Questionnaire (FFQ) and Family History Questionnaire (FHQ). Multivariate logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence interval (95%CI) after adjusting potential confounding covariates.

Results:

Result from this study showed that the highest quintile of walking was associated with increased colorectal cancer risk for both males and females in both provinces (highest VS lowest: ON: OR=1.51, 95%CI=1.07-2.13; NL: OR=2.01, 95%CI=1.25-3.22; pooled analysis: OR=1.70, 95%CI=1.09-2.66). However, this result could be biased because a higher proportion of cases responded to this item than controls. Non-walking exercise was not significantly associated with reduced risk of colorectal cancer for both sex and provinces. Total recreational physical activity was not substantially associated with CRC risk.

Conclusions:

These findings suggest that increasing amounts of non-walking exercise suggested a non-significantly reduced risk of colorectal cancer while walking does not. Further large population based prospective studies on physical activity (walking, non-walking, and total activities) are needed to evaluate effective frequency, duration and intensity of physical activity in relation to colon and rectal cancer prevention.

4.2 Introduction

Colorectal cancer (CRC) is the third most common cancer in Canada, with an estimated 22,500 new cases and 9,100 deaths in 2010 [11]. Engaging in physical activity has long been considered as an effective strategy for cancer prevention [12]. Comprehensive reviews found that increased physical activity is a substantial protective factor against colon or colorectal cancer [13-16]. A large number of prospective [17-20] and case-control [21, 22] studies have found statistically significant associations between physical activity and colon cancer, especially for men, while a few studies have examined associations in rectum cancer indicated no significant associations [23-25]. Studies have indicated that physical activity has differential effects on sub-site of colorectal cancer [190-194]. Therefore, the beneficial role of physical activity in the prevention of colon and/or rectal cancer is inconsistent and varied between women and men [17, 21, 25, 26, 150, 151]. The measurement of physical activity in these studies varied and was based on limited type of activity. The type, frequency, duration and intensity of activities are important components of public health knowledge as they pertain to reduce risk of colorectal cancer [12, 26]; however, this kind of information is limited.

Walking is one of the most common forms of moderate level physical activity among

middle-aged and older people [195]. Its impact on CRC risk has only been examined by a few studies [196-198]. Guidelines from the WHO Library Cataloguing in Publication Data [199], Centers for Disease Control and Prevention, American College of Sports Medicine [200], as well as the Surgeon General's Report on Physical Activity and Health[201], all recommended at least 30 minutes of moderate intensity physical activity on five or more days a week and advise some regular vigorous exercise for better health. This differs from earlier guidelines that advised vigorous exercise for at least 20 minutes three or more times per week [202]. Although the guidelines can be easily met by most of the population, the potential benefits of moderate intensity physical activity, particularly the specific role of walking in cancer prevention, are unclear. In addition, the actual role of non-walking exercise against colorectal cancer remains relatively unexplored.

The purpose of this paper was to 1) examine the associations of walking, non-walking exercise, total recreational physical activity and colorectal cancer risk using the data-base of a large population based case-control study in Canada; 2) compare the roles of walking, and non-walking exercise in colorectal cancer risk; 3) examine whether different effects of physical activity on colorectal cancer exists between Ontario (ON) and Newfoundland and Labrador (NL).

4.3 Methods

Study population

This study used the data of Newfoundland and Ontario Colorectal Cancer case-control study. Incident CRC cases were recruited from the provincial cancer registries, resulting in the establishment of Ontario Familial Colorectal Cancer Registry (OFCCR) and Newfoundland Familial Colorectal Cancer Registry (NFCCR). Cases aged 20-74 years and

diagnosed during 1997-2000 (phase I), 2003-2006 (phase II) in ON, and 2003-2006 in NL were identified; and their pathology reports were verified by study staff (pathology confirmed ICD 9th revision codes: 153.0-153.9, 154.1-154.3, and 154.8; or ICD-0 codes: 18.0-18.7, 19.9, 20.9).

Controls were a random sample of residents aged 20-74 years old in ON and NL. In Ontario, controls were recruited through a list of residential phone numbers or population-based assessment rolls provided by Bell Canada and the provincial government, respectively. In NL, controls were identified through random digit dialing.

Data collection

Once verbal consent for participation was attained through telephone contact, a survey package was forwarded to each potential participant. The package contained a pamphlet of general information concerning the study, a consent form, a self-administered Personal History Questionnaire (PHQ), Food Frequency Questionnaire (FFQ), Family History Questionnaire (FHQ), and a self-addressed stamped envelope. If a participant did not return complete questionnaires within 6-8 weeks, and a follow-up telephone call were sent to ensure that participants received and returned the study package. A telephone interview or assistance was offered when illiteracy or physical disability was a concern.

Measures of exposure

The PHQ was designed to investigate 74 items of information on participants, addressing detailed demographic characteristics, medical conditions, physical activity, screening history, use of medication, and the consumption of alcohol and tobacco. Among female participants, additional questions regarding reproductive concerns were surveyed. The FFQ administered

in the ON population was the well-known Hawaii FFQ. The FFQ in NL was adapted to address the unique food consumption pattern of that province. The NL FFQ was a revision of the FFQ used in Ontario. Participants were asked to estimate the frequency and portion size of food items one year prior to their diagnosis or participation in this study.

Recreational physical activity was measured using PHQ by the frequency and duration of walking, jogging, running, bicycling, swimming, tennis, squash racquetball, calisthenics, aerobics, vigorous dance, football, soccer rugby, basketball and subjects' self-reported participation in sports during their 20-30's, 30-50's, and 50's and beyond. The questions regarding physical activity were "In your 20's, did you participate regularly in physical activity for a total of at least 30 minutes a week? Please describe your activities below. Walking-yes or no; For how many years? During those months, on average, for how many minutes or hours per week?" The same questions were asked of jogging, running, bicycling, swimming and so on addressing three periods in total (20-30's, 30-50's, and 50's plus). Participants were asked to specify the frequency and duration of activities which our survey questionnaire did not specify but yet participants considered being recreational exercise.

The derived time, taking frequency and duration into consideration, spent on each exercise after the participant reached the age of 20 was multiplied by its specific metabolic equivalents score (METs) to yield a MET-hour score [186, 187]. Average weekly MET hours for walking, non-walking exercise and total recreational physical activity were calculated. Next, walking, non-walking exercise and total recreational physical activity were further divided into quintiles according to percentage distribution of controls ($<$Q20, $<$Q40, $<$Q60, $<$Q80, $\geq$Q80).

For the analysis, participants with implausibly high or low total energy intakes (<2.5% or >2.5%: in NL, 925 and 4700 kcal for men, 1100 and 4900 kcal for women; in ON, 1040 and 5200 kcal for men, 835 and 4100 kcal for women) [183], and the patients who had familial adenomatous polyposis (FAP) and an in-situ tumor were excluded from the analysis. After these exclusions, based on those who completed both the PHQ and FFQ, 3102 subjects (1272 cases and 1830 controls) from ON and 1139 subjects (488 cases and 651 controls) from NL remained for the analysis.

Statistical analysis

Potential confounding covariates were selected based on their observed relationships to colorectal cancer through Chi-square testing ($P<0.10$) and previous studies that suggested plausible associations with physical activity and colorectal cancer. Covariates included in the final multivariate model were age; sex; household income (<12,000, 12,000-29,999, 30,000-49,999, ≥50,000); education (lower than high school, high school graduate, college, bachelor or higher); marital status (married, single or never married, separated or divorced or widowed); diabetes (yes or no); hypercholesterolemia (yes or no); use of aspirin (yes or no), non-steroidal anti-inflammatory drugs (yes or no), laxatives (yes or no), and alcohol (unit in gram); total intake of iron (unit in milligram), calcium (unit in milligram), vitamin D (unit in microgram), dietary fibre (unit in gram), folate acid (unit in microgram) and saturated fat (unit in gram); total energy intake (kCal); pack years of smoking (<1 year, <10, <20, <40, ≥40); Body Mass Index (underweight<18.5, normal18.5-25, overweight≥25) and BMI change (BMI 2 years before diagnosis minus BMI in their 20's).

Descriptive statistics were used to compare characteristics of cases and controls. The study used multivariate logistic regression to estimate Odds Ratios (OR) and a 95%

Confidence Interval (95%CI) of the associations between different levels of walking, non-walking, total recreational physical activity and colorectal cancer after adjusting for potential confounders. *P* values for linear trend were assessed by modeling the median value of each category (MET hours per week) of walking, non-walking, and total recreational activities. The interactions between quintiles of physical activity and Body Mass Index (underweight<18.5, normal18.5-25, overweight≥25) were evaluated. All tests of statistical significance were two-sided. SAS 9.1 has been used in statistical analysis (version 9.1 SAS Institute, Cary, NC, USA).

4.4 Results

Participant characteristics

The final analysis included 1272 cases and 1830 controls in Ontario, 488 cases and 651controls in NL. There was no sex difference between cases and controls in both provinces. In Ontario, cases were younger than controls and had higher proportions of diabetes; first degree relatives with CRC; laxatives use; non-steroidal anti-inflammatory drugs use; overweight at the age of 20s; polyps; dietary intakes of energy, iron, and total saturated fat; yet lower dietary intakes of calcium and vitamin D; lower percentage of CRC screening; and lower educational level. In NL, cases were older and had higher rates of diabetes; first degree relatives with CRC; former and/or current smoking; laxatives use; overweight; polyps; and dietary intakes of total energy, iron, and total saturated fat; but lower dietary intakes of vitamin D; lower percentage of CRC screening; lower education level and lower household income. See Table 4.6.1 for details.

In Ontario, men who fell into different recreational physical activity levels had significantly distinct dietary intake levels of total energy, saturated fat, calcium, vitamin D,

and folic acid, BMI, the proportion of current and/or past smokers, education level and regular multivitamin use. For Ontario women, the proportion on hormone replacement treatment; the regular use of multivitamin supplement; and the dietary consumption of total energy, calcium, vitamin D, folic acid, fruits and vegetables substantially varied across physical activity levels. In NL, men who were in different categories of physical activity appeared to have different levels of education, income, dietary intake of total energy and saturated fat intake. For NL women, education level; income; and dietary intakes of vitamin D, fruits and vegetables varied with quintiles of physical activity. See Table 4.6.2 and 4.6.3 for details.

For men in Ontario, age-adjusted regression analysis suggested that the highest quintile of walking was related to an increase in risk of colorectal cancer (OR=1.37, 95%CI=1.00-1.89); non-walking exercise was inversely associated with risk of colorectal cancer although the associations were not statistically significant (Odds Ratios, 1.00, 0.79, 0.59, 0.75, 0.95, respectively); and no dose-response relationship was observed (*P* for trend 0.34); for increasing total physical activity levels, only the second and the third quintiles of exercise were significantly associated with reduction in risk (OR=0.71, 95%CI=0.51-0.98; OR=0.63, 95%CI=0.46-0.88). Multivariable analysis showed that no significant associations were observed between walking, non-walking exercise, total recreational physical activity and CRC risk. The overall directions of associations examined in multivariable analysis were similar with that in age-adjusted regression analysis. See Table 4.6.4 for details.

For women in Ontario, the highest level of walking in multivariable analysis was significantly associated with increased CRC risk (OR=1.75, 95%CI=1.01-3.00) while the second quintile of total recreational physical activity in age-adjusted regression analyses

reduced the CRC risk (OR=0.73, 95%CI=0.53-1.00). All other age-adjusted analyses and multivariable analyses showed non-significant associations of CRC risk as in males. Therefore, a combined analysis of both sexes was done to examine possible overall associations. As was found in the individual analysis of men and women, the highest level of walking in multivariable analysis was significantly associated with increased CRC risk (OR=1.51, 95%CI=1.07-2.13). Non-walking exercise was inversely associated with reduced CRC risk but the associations were non-significant. See Table 4.6.4 for details.

In NL, the overall risk reductions for walking, non-walking exercise and total physical activity were not significant with the exception that the highest level of walking was associated with increased CRC risk for men in age-adjusted regression analysis (OR=2.10, 95%CI=1.31-3.39), multivariable analysis (OR=2.28, 95%CI=1.28-4.05) and the combined sexes group in multivariable analysis (OR=2.01, 95%CI=1.25-3.22). Although non-walking exercise was linked to CRC risk reduction, only the fourth quintile compared to the lowest quintile showed the significant reduced risk for women in age-adjusted regression analysis (OR=0.53, 95%CI=0.29-0.98). See Table 4.6.5 for details.

The results of the ON and NL populations were similar; therefore, a pooled analysis was performed to examine the effects of walking, non-walking exercise, and total recreational physical activity on CRC. Results from this investigation showed that the highest quintile of walking was associated with increased colorectal cancer risk for both males and females in both provinces (highest VS lowest: OR=1.70, 95%CI=1.09-2.66). Non-walking exercise was not significantly associated with reduced risk of colorectal cancer for both sexes and provinces. Middle levels of total recreational physical activity were not substantially associated with CRC risk reduction while the 5th quintile of total recreational physical activity

suggested an increased risk of colorectal cancer (highest VS lowest: OR=1.10, 95%CI=0.86-1.41). See Table 4.6.6 for details.

When considering that exercise may have differential effect on colon and rectum cancers, we additionally performed extra sub-site analysis. In ON, walking was associated with borderline significantly increased rectum risk for men (OR=1.02, 95%CI=1.00-1.04, *P* for trend 0.04) and the combined sexes group (OR=1.01, 95%CI=1.00-1.03, *P* for trend 0.05) but not for women. In NL, the highest level of walking was associated with increased rectum cancer for men (OR=3.39, 95%CI=1.64-7.01), women (OR=7.27, 95%CI=1.53-34.45) and both sexes (OR=3.71, 95%CI=1.98-6.96). The details are not shown in tables.

4.5 Discussions

In this large Canadian population based case-control study, we found that non-walking exercise were indicated to be inversely associated with lower risk of colorectal cancer while the highest level of walking and total recreational activity were linked to an increased colorectal cancer risk in both Ontario and Newfoundland and Labrador.

Walking is a common form of moderate exercise [195, 199]; however, only a few studies have been implemented to investigate its role in cancer prevention. The evidence that walking alone can be considered as an effective cancer prevention strategy is inconsistent [12, 25, 196, 203]. One cohort study in Japan indicated that walking daily was inversely associated with colon risk in men but not women [203]. The same study found that walking did not reduce the risk of rectal cancer [203]. However, the statistical power in this study is limited because of its small sample of cases [203]. Another two prospective studies were not able to demonstrate that walking as a sole means of exercise had a significant beneficial role in

colorectal cancer prevention [12, 25]. Studies have also indicated that a vigorous walking pace was more useful in CRC prevention as compared to a longer time spent walking [25, 204].

The phenomenon seen in the results of this study that the highest category of walking was associated with higher CRC risk was unexpected. It may be explained by several estimations but there was no sufficient evidence. From the aspect of data collection, recall and differential bias could exist in this case-control study, which may have resulted in misclassified physical activity levels for participants. Since walking is a common exercise, it was possibly more common for participants to report inaccurate levels. In total, 32.11% cases and 32.38% of controls have missing information or reported an extremely low level ($\leq$0.05 MET hours per week) of exercise. The validity of this study could be compromised due to large amounts of missing information on main exposures. In addition, cases were aware of their disease status; hence, they were more willing to report their past exposures compared to controls. It is also possible that there are some covariates that have a greater impact on CRC risk than physical activity when physical activity reaches certain levels since we only found the highest level of walking was associated with an increased CRC risk. Thun et al [20] found that physical activity is a weaker protective factor in the prevention of colorectal cancer compared to aspirin use and dietary intake of vegetables and grains . Not all of the studies found consistent beneficial effect of leisure time activity [17]. In addition, the NL population has higher genetic predisposition for CRC and more unique lifestyle factors as compared to many other population groups, even within Canada [180, 205]. This may have more relevance than physical activity to CRC prevention. Besides, this study did not collect information on the walking pace, which is a key measurement of intensity for walking. This lack of detailed information may influence the results as well. Occupational physical activity

was not included in the analysis because the data regarding occupational physical activity was not available for this analysis. Hopefully, education levels and incomes could explain a proportion of the variation associated with the occupation.

A large body of literature suggests that intense activity is needed to decline the colorectal cancer risk and approximate 3 to 4 hours per week is required to reduce the risk [12, 18, 151, 192, 199, 206]. Slattery [192] reported that lower risk of colon cancer was found to be associated with long term vigorous but not moderate activity. Another study has indicated that association was strongest for intense activities among men [26]. Chao et al [207] indicated that walking plus performing other activities showed more clear risk reduction than walking alone . Our study observed non-walking exercise (which is composed of vigorous exercise and other types of physical activity except walking) had a much stronger association with CRC risk reduction than walking alone, which is consistent with these studies. Our preliminary analysis found that cases and controls took part in similar amounts of non-walking exercise in this study; therefore, the non-significant associations between non-walking exercise, total recreational physical activity and CRC risk were acceptable in this study.

Many past studies have found that physical activity in general was an independent factor of colorectal cancer prevention [12, 15, 20, 24, 208]. Studies have also suggested that physical activity is beneficial for the prevention of colon cancer but no similar results were found for rectal cancer [24, 196, 208]. Two studies have shown that increased physical activity was linked with a non-significant increase in CRC risk [18, 209]. One meta-analysis indicated that physical activity was not associated with decreased risk of rectal cancer [14]. We only observed that the highest level of walking was associated with rectal cancer in men,

women and both sexes combined groups. We did not find that the interactions of physical inactivity and obesity together affect the risk of CRC. This is consistent with results from another study, which suggested physical activity is independently associated with CRC risk rather than acting through BMI [12].

Several biological mechanisms have been proposed to explain the association between physical activity and colorectal cancer. Physical activity shortens the fecal transit time; therefore, decreases the exposure time of epithelium to carcinogens [210]. Physical inactivity is associated with insulin resistance and a hyper-insulinemic state which leads to colorectal cancer through growth factors [211]. Physical activity may act through the immune system to produce anti-inflammatory cytokines and an increase of cytokine inhibiters [212-215]that inhibit colonic cell proliferation and decrease colonic motility. Vigorous physical activity is needed for stimulation of the vagus nerve responsible for increasing propulsion [216, 217], which supports the observation that intense activities are most protective.

Some colorectal cancer case-control studies examined the most recent physical activity; however, these studies did not investigate a long term physical activity as we did in this study. In this large Canadian population based case-control study of colorectal cancer, we investigated participant's self-reported exercise from the age of 20 with specific, details on type, frequency and duration of exercise allowing MET hours of exercise per week to be calculated. In addition, we collected information on demographic characteristics, diet, family history medical conditions, and lifestyles through self-administrated questionnaires [180, 205]. The study enabled us to investigate multiple potential confounders and effect modifiers.

As in most of the case-control studies, selection bias should be a concern because

controls might care more about their healthy lifestyles and consequently be much more willing to participate in this kind of study. Another limitation of this study is the ability of the study subjects to accurately recall their past physical activity or even their other lifestyle factors that are used as covariates in our study. Currently, better techniques are not yet available to monitor physical activity in large population groups and physical activity has been proven to be important; therefore should be monitored thus we have little choice but to collect data through self-administered questionnaires. Differential misclassification of physical activity reports between cases and controls may exaggerate the increased risk of exercise in this study. Both the selection and recall bias impact the reliability and validity of findings. Future prospective cohort studies could minimize these bias and provide more reliable data.

Our results show that increasing amounts of non-walking exercise non-significantly reduces the risk of colorectal cancer. Walking alone does not seem to be a strong effective strategy for the prevention of colorectal cancer. The frequency, duration and intensity of exercise appear to be important and should be considered when making public health recommendations. Further population based prospective studies on physical activity are needed to evaluate the effect of frequency, duration and intensity of physical activity in relation to colon and rectal cancer prevention.

4.6 Tables

Table 4.6.1 Selected demographic and lifestyle characteristics of cases and controls of the

colorectal cancer case-control study in Canada

Characteristics	Ontario		Newfoundland and Labrador	
	Case (N=1272)	Control (N=1830)	Case (N=488)	Control (N=651)
Number of participants	1272	1830	488	651
Age (years) [a]	58.4±10.9*	61.5±9.6	61.9±9.0*	59.8±9.4
Polyps [b]	626(49.2)*	180(9.8)	235(48.0)*	84(12.9)
Nonsteroidal anti-inflammatory drugs use [b]	433(34.0)*	787(43.0)	164(33.5)	252(38.7)
Any laxatives use [b]	237(18.6)*	191(10.4)	40(8.2)*	35(5.3)
Current and/or past smoker [b]	733(57.6)	1078(58.9)	353(72.3)*	400(61.5)
Overweight	769(62.4)	1032(60.1)	346(71.0)*	441(67.8)
Overweight in 20 years old [b]	266(20.9)*	290(15.8)	98(20.1)	113(17.4)
Higher Household income [c]	570(44.8)	868(47.4)	118 (24.2)*	241(37.0)
Higher Education [c]	706(55.5)*	1092(59.7)	181 (37.1)*	353(54.2)
First degree relatives with CRC(%) [b]	341(26.8)*	223(12.2)	163 (33.4)*	114(17.5)
Reported any screening [b]	199(15.6)*	476(26.0)	60 (12.3)*	145(22.3)
Total energy intake (kCal/day) [a]	2266.0±796.1*	2161.5±757.7	2367.0±838.2*	2236.3±744.9
Fibre intake [a]	25.5±10.7	25.5±11.3	21.2±9.6	21.7±11.3
Iron intake [a]	30.5±40.8*	25.1±22.8	22.4±90.3*	18.6±33.1
Total saturated fatty acid [a]	27.5±12.2*	25.7±11.7	28.4±12.8*	26.6±12.1
Alcohol consumption [a]	14.8±27.9	13.9±24.1	9.2±22.4	7.8±20.0
Calcium intake [a]	1163.7±565.0*	1213.1±623.3	976.4±515.7	1040±571.8
Vitamin D intake [a]	8.1±5.6*	8.7±6.1	8.00±6.4*	9.2±7.5
Folate acid intake [a]	967.3±542.7	1007.4±596.2	384.3±206.5*	423.2±239.3

[a] Continuous variables were presented as mean±SD(standard deviation). The differences between cases and controls were based on t-tests.

[b] Categorical variables were presented as number(%). The differences between cases and controls were based on chi-square tests.

[c] High level of education included some college, university or post-secondary school; High household income included an average household income>$50,000/year.

* Significant difference between cases and controls ($p \leq 0.05$).

Table 4.6.2 Selected demographic and lifestyle characteristics of cases and controls among men by province and physical activity level [a b]

Characteristics	Ontario					Newfoundland and Labrador				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Number of participants	314	305	309	345	338	139	109	133	140	159
Mean age (years)	61.3	61.0	60.5	61.5	62.0	63.0	61.6	61.4	62.0	61.8
Mean BMI (kg/m2)	27.5	26.3	27.2	26.9	27.3*	28.4	27.2	28.0	27.4	27.9
Polyps (%)	30.8	24.2	24.2	26.0	31.3	31.8	27.6	30.3	30.9	32.7
Regular Multivitamin use (%)	28.0	35.4	38.2	37.5	31.2*	16.8	17.4	14.4	20.0	22.2
Current and/or ever smokers (%)	68.3	69.0	62.7	63.3	68.6*	82.4	77.1	75	70.5	72.8
Higher education (%)[c]	54.1	64.9	65.1	59.7	55.0*	40.3	52.3	57.9	53.6	33.3*
Higher income (%)[c]	36.6	38.4	38.2	37.1	34.9	25.9	39.5	38.4	35.0	26.4*
First degree relatives with CRC (%)	15.6	18.4	15.2	13.6	20.1	23.7	23.9	26.3	24.3	23.3
Reported any screening (%)	27.1	26.9	26.2	23.8	24.0	16.9	16.4	19.6	19.4	17.8
Mean daily intakes										
Fruit servings per week	9.0	9.3	10.0	9.4	9.8	7.9	9.3	8.5	8.4	8.5
Vegetables servings per week	10.3	11.0	11.0	11.7	10.9	9.8	9.6	9.5	10.2	10.9
Red meat servings per week	4.2	4.4	4.4	4.7	4.7	3.8	3.3	3.4	3.6	4.0
Total energy intake (Kcal/day)	2333.5	2284.7	2460.2	2358.3	2576.2*	2311.4	2311.3	2319.5	2488.4	2577.1*
Total fibre	24.2	25.1	26.7	26.0	27.5*	20.7	21.7	21.1	21.9	22.3
Iron	22.8	25.4	26.2	27.7	26.8	18.1	19.7	31.7	17.7	31.4
Saturated fat	27.9	27.1	29.4	29.0	31.5*	27.5	27.9	27.4	30.1	32.0*
Alcohol (g)	20.9	17.9	21.7	18.0	21.7	12.4	9.5	16.6	18.2	15.3
Calcium	1004.9	1046.8	1151.1	1126.8	1170.6*	898.8	973.3	996.2	1032.6	1000.9
Vitamin D	7.0	8.5	8.4	8.7	8.5*	8.3	9.3	9.0	9.1	8.7
Folate acid	893.9	983.1	1031.0	1046.7	1005.2*	359.8	396.1	385.3	392.0	391.1

[a] Continuous variables were presented as means. Category variables were presented in proportions.

[b] Categorical variables were presented as number(%). The differences between cases and controls were based on chi-square tests.

[c] High level of education included some college, university or post-secondary school; High household income included an average household income>$50,000/year.

* Significant difference between cases and controls ($p \leq 0.05$).

Table 4.6.3 Selected demographic and lifestyle characteristics of cases and controls among women by province and physical activity level [a b]

Characteristics	Ontario					Newfoundland and Labrador				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
No of participants	344	306	304	264	273	98	116	92	87	66
Mean age (years)	59.1	58.6	58.3	59.3	60.3	60.8	60.6	59.6	60.9	61.4
Mean BMI (kg/m2)	26.3	26.1	25.7	25.4	25.8	27.4	26.3	27.2	26.7	27.1
Polyps (%)	23.6	19.0	28.6	27.8	21.5*	22.7	27.0	20.0	24.4	25.0
Regular Multivitamin supplement use (%)	36.0	44.8	43.7	48.3	42.3*	16.7	33.6	29.4	26.4	22.7
Current smokers (%)	20.0	17.8	14.5	15.3	13.7	16.3	15.7	14.1	16.3	21.2
Higher education (%)[c]	49.7	58.8	59.2	65.5	48.7*	32.7	61.2	53.3	51.7	28.8*
Higher income (%)[c]	33.7	37.6	37.5	37.5	28.6	22.5	37.1	37.0	34.5	13.6*
First degree relatives with CRC (%)	19.5	18.6	19.4	21.6	20.9	30.6	25.9	19.6	21.8	22.7
Reported any screening (%)	15.7	22.6	17.1	18.6	14.3	20.4	13.8	22.8	16.1	16.7
Hormones replace treatment (%)	31.7	42.9	49.2	43.6	37.4*	39.2	34.8	33.7	34.9	22.8
Mean daily intakes										
Fruit servings per week	11.0	12.2	14.0	13.7	13.7*	10.6	13.1	13.4	14.4	11.1*
Vegetables servings per week	13.8	15.8	16.8	18.0	16.5*	11.9	14.3	15.4	15.1	10.8*
Red meat servings per week	4.3	4.1	3.8	3.9	3.7	3.4	3.4	4.0	3.0	3.4
Total energy intake (Kcal/day)	1941.9	1923.4	2039.5	1960.1	2088.5*	2206.5	2361.7	2203.9	2249.5	2365.7
Total fibre (g/day)	23.4	23.3	26.1	25.7	27.1*	21.6	24.6	23.1	24.4	24.0
Iron (mg/day)	31.0	24.4	30.4	29.7	28.8	27.7	19.0	33.8	28.3	27.1
Saturated fat (g/day)	23.2	23.5	23.9	22.7	24.7	27.8	27.9	26.8	25.9	28.3
Alcohol (g/day)	7.7	8.1	5.8	10.7	7.5	2.1	4.6	3.3	4.1	2.6
Calcium (mg/day)	1202.0	1207.6	1382.0	1368.1	1322.4*	1035.7	1306.8	1170.8	1186.3	1110.4
Vitamin D (mg/day)	8.1	8.2	9.4	9.1	9.1*	7.7	11.1	9.4	11.8	9.1*
Foliate acid (mg/day)	896.2	940.0	1029.3	1030.8	1073.5*	370.3	472.5	438.7	479.7	429.6

[a] Continuous variables were presented as means. Category variables were presented in proportions.

[b] Categorical variables were presented as number(%). The differences between cases and controls were based on chi-square tests.

[c] High level of education included some college, university or post-secondary school; High household income included an average household income>$50,000/year.

* Significant difference between cases and controls ($p \leq 0.05$).

Table 4.6.4 Odds ratio and 95% CI for the association between physical activity and colorectal cancer risk stratified by sex in Ontario

Quintile (MET hours per week)	Men				Women				Women & men
	Cases[a] (N=637)	Controls (N=974)	Age adjusted OR (95%CI)[bc]	Multivariate OR (95%CI)[d]	Cases (N=635)	Controls (N=856)	Age adjusted OR (95%CI)[bc]	Multivariate OR (95%CI)[d]	Multivariate OR (95%CI)[d]
Walking									
Q1	21.7	22.4	1.00	1.00	15.9	19.1	1.00	1.00	1.00
Q2	17.7	17.0	1.17 (0.84-1.64)	0.88 (0.53-1.46)	24.2	21.7	1.31 (0.94-1.84)	1.51 (0.92-2.47)	1.15 (0.82-1.61)
Q3	17.1	19.8	1.03 (0.74-1.44)	0.88 (0.53-1.45)	20.2	22.1	1.08 (0.76-1.54)	1.64 (0.99-2.71)	1.16 (0.82-1.64)
Q4	17.9	19.8	1.09 (0.78-1.53)	1.22 (0.73-2.02)	22.7	19.9	1.31 (0.92-1.87)	1.48 (0.88-2.49)	1.29 (0.91-1.83)
Q5	25.6	21.0	1.37 (1.00-1.89)	1.32 (0.88-2.20)	16.9	17.2	1.16 (0.79-1.70)	1.75 (1.01-3.00)	1.51 (1.07-2.13)
P for trend[e]			0.12	0.06			0.79	0.20	0.03
Non-walking									
Q1	25.0	18.9	1.00	1.00	25.4	23.0	1.00	1.00	1.00
Q2	18.0	19.3	0.79 (0.57-1.11)	0.92 (0.56-1.51)	19.4	20.3	0.99 (0.72-1.38)	0.98 (0.61-1.57)	0.94 (0.67-1.32)
Q3	15.9	22.2	0.59 (0.42-0.84)	0.67 (0.40-1.12)	18.6	19.3	1.00 (0.71-1.40)	1.01 (0.62-1.65)	0.84 (0.59-1.19)
Q4	19.1	20.8	0.75 (0.54-1.06)	0.81 (0.48-1.35)	18.6	18.5	1.07 (0.75-1.52)	0.94 (0.57-1.54)	0.89 (0.63-1.27)
Q5	22.0	18.8	0.95 (0.67-1.33)	0.77 (0.47-1.29)	18.1	18.9	1.04 (0.73-1.48)	0.87 (0.53-1.44)	0.85 (0.60-1.20)
P for trend[e]			0.34	0.55			0.78	0.53	0.46
Total activity									
Q1	21.8	18.0	1.00	1.00	24.3	22.2	1.00	1.00	1.00
Q2	17.4	19.9	0.71 (0.51-0.98)	0.95 (0.58-1.55)	18.1	22.3	0.73 (0.53-1.00)	0.94 (0.60-1.47)	0.95 (0.68-1.31)
Q3	16.6	20.8	0.63 (0.46-0.88)	0.96 (0.59-1.55)	20.8	20.1	0.93 (0.68-1.27)	1.02 (0.65-1.60)	0.98 (0.71-1.36)
Q4	20.0	22.4	0.73 (0.53-1.01)	1.04 (0.64-1.67)	18.1	17.4	0.96 (0.69-1.33)	0.90 (0.56-1.45)	0.96 (0.69-1.34)
Q5	24.2	18.9	1.08 (0.79-1.48)	1.24 (0.79-1.96)	18.7	18.0	0.98 (0.71-1.36)	1.02 (0.65-1.60)	1.15 (0.84-1.58)
P for trend[e]			0.045	0.21			0.46	0.90	0.25

[a] The number of cases and controls in quintiles were represented as percentage.

[b] OR: Odds Ratio; 95% CI: 95% confidence interval.

[c] Adjusted for age, walking and non-walking exercise are mutually adjusted.

[d] Adjusted for age, diabetes, BMI, first-degree relatives with CRC, polyps, smoking status, regular NSAID use, colorectal cancer screening, inflammatory colitis, daily total energy intake, total fibre, calcium, iron, foliate acid, vitamin D, total saturated fatty acid intake, alcohol drinking, education attainment, household income, and hormone replacement treatment in women.

[e] Linear trend was tested by modeling physical activity as continuous variables by using the median value of each category.

Table 4.6.5 Odds ratio and 95% CI for the association between physical activity and colorectal cancer risk stratified by sex in NL

Quintile (MET hours per week)	Men				Women				Women & men
	Cases [a] (N=296)	Controls (N=384)	Age adjusted OR (95%CI) [bc]	Multivariate OR (95%CI) [d]	Cases (N=192)	Controls (N=267)	Age adjusted OR (95%CI) [bc]	Multivariate OR (95%CI) [d]	Multivariate OR (95%CI) [d]
Walking									
Q1	20.6	25.1	1.00	1.00	18.9	12.9	1.00	1.00	1.00
Q2	21.3	20.0	1.36 (0.84-2.20)	1.37 (0.76-2.50)	17.3	20.2	0.60 (0.31-1.15)	0.76 (0.34-1.72)	1.11 (0.70-1.78)
Q3	13.2	15.5	1.07 (0.63-1.83)	1.19 (0.62-2.30)	24.6	31.2	0.60 (0.33-1.10)	0.74 (0.34-1.60)	0.96 (0.59-1.54)
Q4	13.5	20.5	0.87 (0.52-1.47)	0.84 (0.44-1.60)	22.5	24.3	0.72 (0.39-1.36)	1.04 (0.47-2.31)	0.95 (0.59-1.54)
Q5	31.4	18.9	2.10 (1.31-3.39)	2.28 (1.28-4.05)	16.7	11.4	1.15 (0.56-2.36)	1.76 (0.71-4.40)	2.01 (1.25-3.22)
P for trend [e]			0.004	0.004			0.29	0.07	0.001
Non-walking									
Q1	19.2	19.0	1.00	1.00	27.1	21.4	1.00	1.00	1.00
Q2	17.9	17.7	0.82 (0.48-1.38)	0.71 (0.37-1.38)	22.4	22.8	0.82 (0.47-1.44)	0.77 (0.38-1.56)	0.72 (0.45-1.15)
Q3	20.3	21.6	0.80 (0.48-1.34)	0.98 (0.52-1.85)	15.6	19.5	0.67 (0.36-1.25)	0.56 (0.26-1.24)	0.84 (0.52-1.35)
Q4	18.6	21.1	0.70 (0.41-1.19)	0.97 (0.50-1.87)	16.2	21.7	0.53 (0.29-0.98) *	0.63 (0.29-1.37)	0.80 (0.49-1.29)
Q5	24.0	20.6	0.89 (0.53-1.50)	0.91 (0.47-1.75)	18.7	14.6	0.92 (0.49-1.71)	0.56 (0.25-1.28)	0.77 (0.47-1.26)
P for trend			0.89	0.97			0.93	0.25	0.58
Total activity									
Q1	21.0	20.0	1.00	1.00	24.0	19.5	1.00	1.00	1.00
Q2	14.2	17.5	0.80 (0.48-1.34)	0.82 (0.43-1.56)	25.0	25.5	0.80 (0.46-1.38)	1.06 (0.52-2.17)	0.89 (0.56-1.40)
Q3	18.2	20.6	0.88 (0.54-1.43)	0.93 (0.51-1.70)	16.7	22.5	0.62 (0.35-1.12)	0.78 (0.37-1.65)	0.82 (0.52-1.30)
Q4	18.2	22.4	0.80 (0.49-1.29)	0.85 (0.47-1.55)	19.3	18.7	0.83 (0.46-1.50)	1.30 (0.60-2.83)	0.95 (0.60-1.50)
Q5	28.4	19.5	1.44 (0.91-2.28)	1.47 (0.82-2.63)	15.1	13.9	0.87 (0.46-1.64)	0.62 (0.27-1.45)	1.12 (0.71-1.77)
P for trend			0.02	0.06			0.96	0.35	0.33

[a] The number of cases and controls in quintiles were represented as percentage.

[b] OR: Odds Ratio; 95% CI: 95% confidence interval.

[c] Adjusted for age, walking and non-walking exercise are mutually adjusted.

[d] Adjusted for age, diabetes, BMI, first-degree relatives with CRC, polyps, smoking status, regular NSAID use, colorectal cancer screening, inflammatory colitis, daily total energy intake, total fibre, calcium, iron, foliate acid, vitamin D, total saturated fatty acid intake, alcohol drinking, education attainment, household income, and hormone replacement treatment in women.

[e] Linear trend was tested by modeling physical activity as continuous variables by using the median value of each category.

Table 4.6.6 Odds ratio and 95% CI for the association between physical activity and colorectal cancer stratified by sex in Ontario and NL

Quintile (MET hours per week)	Men Cases [a] (N=933)	Controls (N=1358)	Age adjusted OR (95%CI)[bc]	Multivariate OR (95%CI) [d]	Women Cases (N=827)	Controls (N=1123)	Age adjusted OR (95%CI)[bc]	Multivariate OR (95%CI)[d]	Women & men Multivariate OR (95%CI)[d]
Walking									
Q1	21.0	22.4	1.00	1.00	15.9	17.2	1.00	1.00	1.00
Q2	19.2	18.6	1.16 (0.89, 1.52)	1.00 (0.69, 1.45)	23.1	21.7	1.14 (0.84, 1.53)	1.19 (0.79, 1.80)	1.19 (0.79, 1.80)
Q3	15.0	17.7	1.00 (0.75, 1.33)	1.08 (0.73, 1.61)	20.1	22.7	0.98 (0.72, 1.33)	1.33 (0.88, 2.03)	1.32 (0.87, 2.00)
Q4	15.4	18.8	0.98 (0.73, 1.30)	1.00 (0.67, 1.49)	21.8	21.4	1.12 (0.82, 1.52)	1.22 (0.80, 1.87)	1.22 (0.79, 1.86)
Q5	29.4	22.5	1.50 (1.16, 1.95)	1.64 (1.16, 2.31)	19.1	17.0	1.27 (0.91, 1.76)	1.69 (1.08, 2.65)	1.70 (1.09, 2.66)
P for trend			0.01	<0.01			0.20	0.05	<0.01
Non-walking									
Q1	23.9	19.6	1.00	1.00	26.6	23.3	1.00	1.00	1.00
Q2	17.8	18.8	0.81 (0.61, 1.07)	0.77 (0.52, 1.13)	20.3	20.8	0.95 (0.72, 1.26)	0.93 (0.64, 1.36)	0.93 (0.64, 1.37)
Q3	16.0	20.8	0.64 (0.48, 0.85)	0.79 (0.53, 1.16)	16.8	18.3	0.88 (0.65, 1.18)	0.87 (0.58, 1.31)	0.88 (0.58, 1.31)
Q4	18.5	20.5	0.74 (0.56, 0.98)	0.79 (0.53, 1.16)	17.8	18.7	0.91 (0.67, 1.23)	0.85 (0.57, 1.28)	0.86 (0.57, 1.28)
Q5	23.7	20.3	0.91 (0.69, 1.20)	0.80 (0.55, 1.17)	18.5	18.9	0.92 (0.68, 1.25)	0.80 (0.54, 1.21)	0.81 (0.54, 1.21)
P for trend			0.50	0.16			0.71	0.33	0.29
Total activity									
Q1	22.1	19.0	1.00	1.00	24.8	22.7	1.00	1.00	1.00
Q2	15.5	18.5	0.71 (0.54, 0.94)	0.85 (0.58, 1.24)	18.7	21.4	0.80 (0.61, 1.05)	1.07 (0.74, 1.55)	0.94 (0.72, 1.22)
Q3	16.5	19.8	0.70 (0.53, 0.92)	0.89 (0.61, 1.29)	19.0	19.9	0.86 (0.65, 1.13)	1.00 (0.68, 1.46)	0.92 (0.71, 1.20)
Q4	18.9	21.9	0.74 (0.57, 0.96)	0.98 (0.68, 1.40)	18.4	17.4	0.97 (0.73, 1.29)	1.06 (0.72, 1.56)	1.00 (0.77, 1.30)
Q5	27.0	20.8	1.12 (0.87, 1.44)	1.18 (0.84, 1.66)	19.1	18.6	0.96 (0.73, 1.27)	0.99 (0.68, 1.45)	1.10 (0.86, 1.41)
P for trend			0.01	0.09			0.61	0.90	0.22

[a] The number of cases and controls in quintiles were represented as percentage.

[b] OR: Odds Ratio; 95% CI: 95% confidence interval.

[c] Adjusted for age, walking and non-walking exercise are mutually adjusted.

[d] Adjusted for age, diabetes, BMI, first-degree relatives with CRC, polyps, smoking status, regular NSAID use, colorectal cancer screening, inflammatory colitis, daily total energy intake, total fibre, calcium, iron, foliate acid, vitamin D, total saturated fatty acid intake, alcohol drinking, education attainment, household income, and hormone replacement treatment in women.

[e] Linear trend was tested by modeling physical activity as continuous variables by using the median value of each category.

Chapter 5 Project 2: Examining the Direct and Indirect Effects of Socioeconomic Status (SES) on Colorectal Cancer Risk using Structural Equation Modeling

5.1 Abstract

Background:

Existing epidemiologic studies have not investigated how risk factors work together to increase the incidence of colorectal cancer (CRC) so the true effect of each factor could be under- or over estimated. This study explored how socio-economic status (SES) directly influenced the risk of developing CRC and its mediated effect on CRC risk through diet pattern while adjusting for the possible risk factors of alcohol intake, smoking, physical inactivity, and obesity.

Methods:

This study used data collected from an existing population based case-control study of Newfoundland and Labrador, in which data pertaining to personal demographic characteristics, medical history, diet and other lifestyle factors were collected using self-administered questionnaires. Measurement and structural modeling was used to test conceptual models. Exploratory factor analysis was used to identify dietary patterns measured by 39 food groups. Then, the direct and intermediate effects of risk factors were examined using structural equation modeling.

Results:

The results from multivariate regression analysis indicated that age (OR=1.03), SES (OR=0.89), processed meat intake (OR=1.08), no CRC screening (OR=2.67), smoking (OR=1.44, 1.85 (ever, current)), and family history score of CRC (OR=1.06), were significantly associated with the risk of CRC. SES has a direct effect (β=0.05) on the risk of CRC. An indirect effect (β=0.06) of SES on CRC risk also existed by influencing processed

meat intake (β=0.01), vegetables intake (β=0.01), screening frequency (β=0.02), and smoking (β=0.02).

Conclusions:

This study suggested that the NL population has three major dietary patterns: (1) processed meats plus root vegetables; (2) vegetables; and (3) fruits). Structural equation modeling, a relatively new approach to epidemiology studies, provided unique information on the direct effect of socioeconomic status on the development of CRC but also SES's indirect effect through a set of common CRC risk factors.

5.2 Introduction

Colorectal cancer (CRC) is the third most common type of cancer in Canadian males and females [11]. Inherited familial CRC explains about 10%-15% of all CRC cases [51-53]. The majority of CRC cases result from gene-environment interactions [52, 54, 55]. Lifestyle factors such as dietary intakes play an important role in the development of CRC. Considering that 75%- 85% of CRC are sporadic, identifying different pathways of CRC through examining its risk factors is of public health importance. Important modifiable risk factors for CRC include tobacco use, unhealthy diet, physical inactivity and excessive consumption of alcohol [47, 218].

A large number of existing epidemiological studies have investigated the associations of dietary factors [96, 124, 142, 219], physical inactivity [15, 17, 18, 150, 152, 220], smoking [158, 205, 221], alcohol consumption [161, 222, 223], and socioeconomic status [224] with the occurrence of CRC. One major limitation of traditional epidemiologic research is its focus on one major risk factors of interest while controlling for other covariates. This likely over simplifies the complicated and interdependent relationships among various candidate factors

of interest [37]. Consequently, most reported studies have been unable to specify how these candidate risk factors work together to increase the occurrence of CRC and the true effect of each factor would be under-estimated [38-40]. Identifying major dietary patterns through exploratory factor analysis, a relatively new approach in epidemiology, has investigated the intercorrelations of multiple food items/nutrients simultaneously, which has overcome the limitation of partially examining dietary risk factors [225]. Therefore, studies such as this one, which are able to delineate and test how candidate risk factors are interrelated and jointly affect the occurrence of CRC, are expected to provide important insights into exploring the etiology of CRC.

Newfoundland and Labrador (NL) has the highest CRC incidence rate in Canada [11]. The province of NL is the eastern most part of North America. Compared with the rest of Canada, NL is geographically isolated and it has a homogeneous population, estimated to be of 98% English or Irish descent [226]. According to the 2006 Statistics Canada report, the population in NL is about 510,000 with over 40% of the residents living in rural communities [227]. Due to its distinct geography and heritage, NL is known for traditional foods, such as pickled meat and game (wild animal) meat [228]. Residents of NL are more likely to smoke cigarettes and less likely to engage in leisure time physical activity than other Canadians [205]; further, people in NL are believed to eat fewer fruits and vegetables and consume more preserved foods [180]. Given the distinct diet, lifestyles, and high CRC incidence rate, an investigation of the NL population should be ideal to explore the interrelationships of risk factors for CRC [180, 227].

Although the inter-dependent relationships among socioeconomic status (SES), lifestyles, diet, and health have been well recognized [41-43], their complex inter-relationships in

relevance to CRC have not been examined. The proposed research hypothesized that lower SES predisposes people to certain risk factors (e.g. fewer vegetables and fruits consumed, higher proportion of smoking, lower percentage participating in CRC screening, etc), which in turn may interact with genetic factors and lead to the occurrence of colorectal cancer. The objectives of this study were to: 1) explore the potential association among CRC risk factors; 2) posit a conceptual model that delineates the interrelationships with respect to how SES, dietary factors, and lifestyles work together to give rise to CRC; and 3) operationalize the proposed conceptual model using the database of Newfoundland and Ontario Colorectal-cancer Study (NOCS). It is important to note that only the NL data was used in this study.

5.3 Study Population and Methods

5.3.1 Study Population

The Newfoundland Cancer Treatment and Research Foundation data were used to identify newly diagnosed cases of colon or rectal cancer and cases were recruited into the Newfoundland Familial Colorectal Cancer Registry (NFCCR). Pathologists in the study confirmed the pathology reports of cases. Inclusion criteria for cases:

1) Incident primary invasive colon or rectal cancer [pathology confirmed International Classification of Diseases 9th revision codes: 153.0-153.9, 154.1-154.3 and 154.8 (ON & NL); or ICD-10 codes: 18.0-18.7, 19.9, 20.9 (NL only)];
2) Diagnosed between January 1999 and December 2003 in NL;
3) Diagnosed at ages between 20 and 74 years old; and
4) Residents of NL at the time of diagnosis.

Controls recruited by the NFCCR were comprised of a random sample of residents aged

20-74 years through random digit dialing [182]. Within a frequency matched case-control study, controls were 5-year age group and sex matched with the colorectal cancer cases. Initially, a set of 192,000 possible residential telephone numbers were generated and randomly arranged. Research assistants with prior experience in telephone surveying made the initial contacts by dialing those numbers in a sequential order until the desired number of controls was reached. A screening interview of potential control subjects was conducted to identify if any household member was eligible based upon their age, sex and willingness to participate in the study.

5.3.2 Data Collection

Once verbal consent for participation was obtained through telephone contact, a survey package was forwarded to each potential participant. The package included an information pamphlet with general information concerning the study, a consent form, a self-administered Personal History Questionnaire (PHQ), Food Frequency Questionnaire (FFQ), Family History Questionnaire (FHQ), as well as a self-addressed stamped envelope. If a participant did not return the completed questionnaires within three weeks, a follow-up telephone call was made to ensure the study package had been received. A telephone interview or assistance was offered when illiteracy or physical disability was a concern.

The PHQ was designed to investigate 74 items of information on participants including detailed information pertaining to demographic characteristics (age, sex and marital status), bowel screening history, medication use (non-steroidal anti-inflammatory drugs), physical activity (walking, jogging, running etc. both currently and during participant's 20-30's, 30-50's, and 50's+), alcohol consumption , tobacco use (never smoker, former smoker and current smoker), education (less than high school, high school, some college, bachelor or

higher), income (less than $12,000, $12,000-$29,999, $30,000-$49,999, $50,000 and higher), residence(rural or urban) and anthropometric measures (height and body mass index).

The FFQ was adapted from a FFQ for the previously validated multi-ethnic Hawaiian/Southern Californian to incorporate the unique food consumption pattern of the NL population. Participants were asked to estimate the frequency and portion size of 169 food items one year prior to their diagnosis for cases or participation in this study for controls. For each food item, subjects were asked to estimate the frequency of food consumption (daily, weekly, monthly or never) and their usual portion size (average, smaller or larger). Information on vitamin and other dietary supplements was also collected. Dietitians on the study team helped convert the 169 food items into units of daily grams of food for each participant. Foods were also categorized into thirty-nine groups. The food grouping was developed based upon the primary role of foods in the diet and their possible relationships with cancer etiology [141]. Food groups include milk, yogurt, coffee, tea, sugar, soft drinks, egg, cheese, mixed dishes, red meat, game, cured or processed red meat, cured or processed total meat, poultry, fish, processed fish, fruit juice, root vegetables, cruciferous vegetables, total cereals and grains, whole grains, deserts, sweets, vegetables juice, beer, white wine, red wine, liquor, citrus, berries, dried fruit, canned fruit, other fruit, pies, jam and pickled vegetables.

The FHQ collected information on the diagnosed type of cancer or tumour as well as the cancer history of participants. The same questions were asked of the participant's mother, father, children, brothers and sisters, mother's brothers and sisters, father's brothers and sisters and other relatives who had also been diagnosed with cancer. Family history score was derived from collected information [229].

5.3.3 Statistical Analysis

For the analysis, participants with implausibly high or low total energy intakes (<2.5% or >2.5%: 925 and 4700 kcal for men, 1100 and 4900 kcal for women) [181, 230], and the patients who had familial adenomatous polyposis (FAP) or an in-situ tumor were excluded. After these exclusions, based on those who completed both the PHQ and FFQ, 1139 subjects (488 cases and 651 controls) remained for the analysis.

Descriptive statistics (frequency, means and standardized deviations) were used to describe the characteristics of cases and controls. Before the analysis, potential indicators of possible factors were standardized using the Z scores method [231], which is a common way to summarize and standardize data with large variability.

$$\frac{X-\mu}{\sigma}=Z$$

When establishing a measurement model, potential risk factors of CRC that cannot be directly observed or measured were presented as a factor with a factor score, which was the sum of standardized scores (Z scores) of each factor's corresponding indicators that loads on the same factor without considering the weights [231]. SES was measured by education, income and resident region. Although education and income were ordinal variables, Z scores were calculated based on the median value of each category. For the variable of region, Z score was assigned as -0.5 and 0.5 for rural and urban area, respectively.

The dietary pattern was explored by examining the 39 food groups through exploratory factors analysis (EFA), which was used to identify the possible number of factors. The food

groups with factor loadings equal to or greater than 0.25 were considered to comprise its dietary patterns. According to the results of EFA, literature review, and an understanding of dietary patterns in NL, three major dietary patterns were found: (1) processed meats plus root vegetables; (2) vegetables; and (3) fruits). To derive the factor score of processed meats, the sum of the Z scores of red meat, cured/processed (red) meat, fish, processed fish, and root vegetables were calculated. To derive the factor score of the vegetables pattern, the Z scores of cruciferous vegetables, other greens, beans, peas, tomato sauce and other vegetables excluding root vegetables were added. The factor score of fruits intakes was calculated by combining the Z score of citrus fruits, berries, dried fruit and other fruits. In order to explore potentially important risk factors of CRC, the study used binary and multivariable logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95%CI). This was used to explore of the potential associations among age; sex; SES; BMI; family history score of colorectal cancer; history of inflammatory bowel disease; non-steroidal anti-inflammatory drug use; physical activity; history of CRC screening; smoking; intakes of processed meat plus root vegetables; vegetables and fruits. SAS 9.1 was used for the analysis of basic characteristics and regression models (SAS Institute, Cary, NC).

To further explore the possible direct and indirect effects of SES on other potential risk factors, factor analysis and structural equation modeling were performed using 5.1 M-plus software (Muthen & Muthen). The goodness of model fit was evaluated by indices: (1) the Comparative Fit Index (CFI), which is an incremental fit index that assesses model fit compared to a baseline model. It is resistant of non-normality and a small sample size; and a value exceeding 0.9 indicates acceptable model fit [232] while some studies have suggested using 0.95 as a cut-off point[233]; (2) the Tucker Lewis Index (TLI), also known as NNFI, where a recommended good fit value is more than 0.9 [234] or 0.95 [233]; a small sample

size does not influence this index; (3) the root mean square error of approximation (RMSEA), an indicator of the fit of population data to the model, which aims to remove sampling error from model fit. The acceptable level is less than 0.08 or 0.06 [233]. (4) Weighted root mean square residual (WRMR) for categorical data was estimated and its value was less than 1.0 indicating a good fit. (5) Standardized Root Mean Square Residual (SRMR) is a fit index for continuous data. A value less than .08 is generally considered a good fit [233]. The significance level of each path coefficient in the model was evaluated by the *P* value of 0.05.

5.4 Results

5.4.1 Descriptive Characteristics

Important demographic characteristics of the 488 cases and 651controls were presented in Table 5.6.1. A lower proportion of CRC cases participated in CRC screening; were older; a higher proportion of polyps history; and were more likely to be former and/or current smokers; have first-degree relatives with CRC, be overweight, have higher total energy intakes; reside in rural areas, have lower education levels and have lower household incomes.

5.4.2 Exploratory Factors Analysis (EFA)

Preliminary EFA suggested that six factors could represent the dietary pattern. See Table 5.6.2 for details. The model fit indices were: CFI=0.86. TLI=0.80, RMSEA=0.04 and SRMR=0.03. The scree plot is shown in Figure 5.6.1 and factor loadings of EFA are presented in Table 5.6.2. Six potential factors were further reduced to three factors based on the following criteria: (1) deleting factors with cross loadings; (2) deleting factors with less than three indicating variables; (3) considering potential dietary patterns reported in the literature; and (4) understanding of the dietary culture in NL. The final three factors were: (1) processed meat plus root vegetables; (2) vegetables; and (3) fruits. After deleting irrelevant variables based on preliminary EFA, secondary EFA was performed and model fit indices

were: CFI=0.97. TLI=0.93, RMSEA=0.04 and SRMR=0.02. As suggested by model fit indices, factors of processed meat and root vegetables consumption, vegetables intake and fruits intake were adequately measured by the selected variables and well represent the dietary pattern in NL.

5.4.3 Regression Results

Binary regression model of examining SES on CRC risk showed that higher SES reduced the risk of CRC (OR=0.80, 95%CI=0.75-0.86). The results from multivariate regression analysis indicated that age, SES, processed meat intake, non-screening, smoking and family history score of CRC were significantly associated with risk of CRC. See Table 5.6.3.

5.4.4 Structural Equation Modeling

As conceptualized in our theoretical model, the direct and mediated effects of potential risk factors of CRC were tested in SEM (see Figure 5.6.2). Older age (β=-0.01), no CRC screening (β=-0.33), ever or current smokers (β=-0.17), higher family history score of CRC (β=-0.03), processed meat intake (β=-0.04) and non-NSAID use (β=-0.19) increased the risk of CRC. Higher socioeconomic status (β=0.05) and vegetables intake (β=0.03) were linked to reduced risk of CRC.

Being female (β=-0.74) and have a higher SES (β=-0.38) decreased the likelihood of processed meat intake. Older age (β=0.05), being female (β=1.31) and higher SES (β=0.34) were associated with an increased consumption of vegetables. Subjects with a higher SES have a higher chance of participating in CRC screening (β=-0.07) and were less likely to have smoked or to be a current smoker (β=-0.11). SES appeared to have a direct effect on the risk of CRC (β=0.05) and an indirect effect (β=0.06) which existed through a high processed meat intake (β=0.01), lower prudent vegetable intake (β=0.01), fewer CRC screening (β=0.02) and

smoking (β=0.02). Fruit intake appeared to be a protective factor in preventing CRC but it was not included in the final SEM model because of the model fit issue. Model fit indices of path analysis were: CFI=0.59. TLI=0.37, RMSEA=0.08 and WRMR=1.94.

5.5 Discussion

Using the standardized score approach, three dietary patterns have been identified: (1) processed meat plus root vegetables; (2) vegetables; and (3) fruits. These dietary patterns were consistent with previous established dietary patterns in the North American and European population [144, 225]. During the process of identifying dietary patterns, total energy intake adjustment was not completed because other studies indicated the robustness of total energy adjustment when using the dietary patterns approach [225]. When assigning food groups through aggregating hundreds of food items in the FFQ and identifying potential dietary patterns, many subjective decisions were made according to literature reports and our understanding of the culture in NL. Labels of dietary patterns were assigned arbitrarily based on the consideration of data interpretation and understanding of the food culture in NL. However, the limitation of subjective decision was unavoidable because no better techniques are available. Different studies have labeled dietary patterns differently, such as using "Fruits and vegetables" [235] or "Prudent" [236] or "salad" [225] for vegetables and fruit intake while using "high meat consumption" [225] or "westernized" [236] for high consumption of (processed) meat. Some studies suggested possible "sweets" [235] and "alcohol" [235, 237] patterns as having influence on risk of CRC, but neither pattern was obvious in this study.

Based on the results of this population based case-control study, this research supports the hypothesis that potential risk factors work together to increase the occurrence of CRC. The common risk factors studies were dietary factors [96, 124, 142, 219], physical inactivity [15, 17, 18, 150, 152, 220], smoking [205, 221], alcohol consumption [161, 222, 223], and

socioeconomic status [224]. These were examined in structural equation modeling to detail how SES influences these other candidate risk factors and subsequently the development of CRC. Higher SES directly reduced the risk of developing CRC and its mediated effects on CRC risk through diet patterns, smoking status, and CRC screening were suggested. The utilization of structural equation modeling in this study specified the direct and indirect effect of candidate risk factors, which helped to uncover the "web" like associations by measuring a set of variables simultaneously [238]. Due to the complexity of causal model in cancer, this study mainly focused on investigating the direct effect of SES on the development of CRC and its indirect effect through some common risk factors. It is possible that a more comprehensive model would explain data better than our proposed model. Model fit indices of structural equation modeling in this study were lower than what was suggested in the psychological area of the literature. This could be explained by the fact that psychometric measures are usually highly correlated which can be called an underlying "construct" or "factor" or "factor structure" or "trait" [239]; while items measured in epidemiological investigations do not necessarily reflect such a potential structure [225].

Previous studies have indicated that factor analysis of dietary patterns has provided a better understanding of the relationship between diet and cancer than the analysis of single nutrients or foods [144, 148, 225]. To our knowledge, this is the first study utilizing structural equation modeling to explore the epidemiologic etiology of cancer. This could provide more insight into the entangled interrelationships among a series of risk factors. This study only presented one 'corner' of the much larger "web" of associations in cancer etiology. The results in this study presented unique information not only pertaining to the direct of effect of SES on the development of CRC but also its indirect effects through a set of common CRC risk factors. Future research in this area should focus on investigating the interrelations of

obesity, physical inactivity, history of cancer related disease, medication use and other candidate risk factors of developing cancer.

5.6 Figure and Tables

Table 5.6.1 Selected demographic and lifestyle characteristics of cases and controls of the Colorectal cancer case-control study in Newfoundland

Characteristics	Newfoundland and Labrador	
	Case (N=488)	Control (N=651)
Age (year)[a]	61.9±9.0*	59.8±9.4
Male (%)	296 (60.6%)	384 (59.0%)
Marital status		
Single or never married	27 (5.5%)	20 (3.1%)
Currently married or living as married	385 (78.9%)	532 (82.1%)
Separated, divorced or widowed	76 (15.6%)	96 (14.8%)
Missing		3
Polyps [b]	235(48.0)*	84(12.9)
Nonsteroidal anti-inflammatory drugs use [b]	164(33.5)	252(38.7)
Current and/or past smoker [b]	353(72.3)*	400(61.5)
Overweight	346(71.0)*	441(67.8)
Overweight at 20 years of age [b]	98(20.1)	113(17.4)
Higher Household income [c]	118 (24.2)*	241(37.0)
Higher Education [c]	181 (37.1)*	353(54.2)
Region (rural)	278 (57.2%)*	321 (49.5%)
First degree relatives with CRC(%)[b]	163 (33.4)*	114(17.5)
Reported any CRC screening [b]	60 (12.3)*	145(22.3)
Alcohol consumption [a]	9.2±22.4	7.8±20.0

[a] Continuous variables were presented as mean±SD (standard deviation). The differences between cases and controls were based on t-tests.

[b] Categorical variables were presented as number(%). The differences between cases and controls were based on chi-square tests.

[c] High level of education included some college, university or post-secondary school; High household income included an average household income>$50,000/year.

* Significant difference between cases and controls ($p \leq 0.05$).

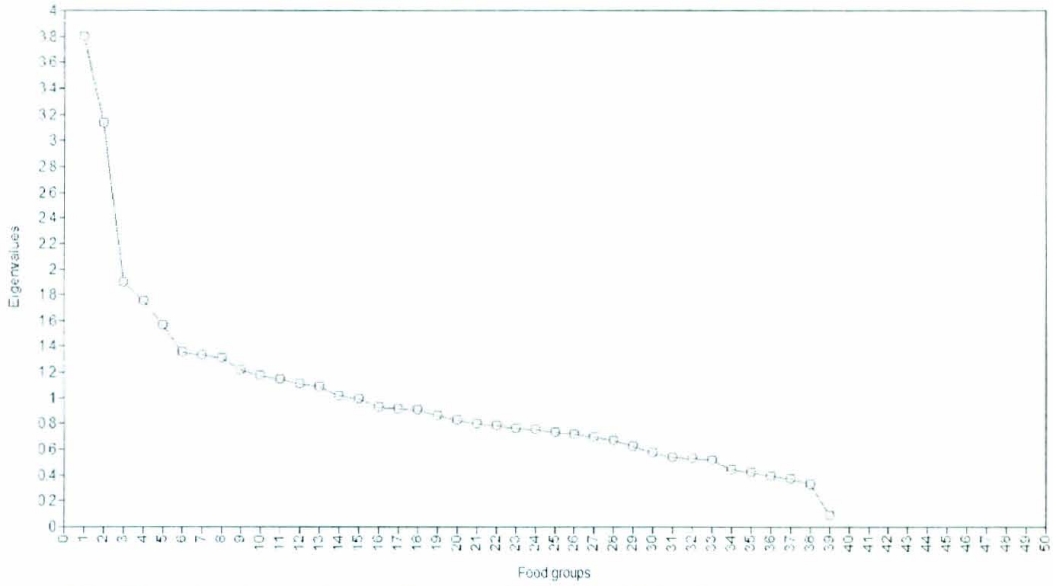


Figure 5.6.1 Eigenvalues for exploratory factor analysis among 39 food groups

Table 5.6.2 Factor loadings of dietary pattern in exploratory factor analysis of the NOCS (Newfoundland)

	Mixed	Processed meat	Meat	Prudent vegetables	Fruit	High sugar
Milk	0.08	-0.02	-0.03	0.18	0.02	0.01
Yogurt	0.03	0.00	-0.01	0.19	0.13	-0.02
Coffee	-0.47	-0.04	0.20	0.04	-0.01	0.05
Tea	0.60	-0.02	0.01	0.01	-0.04	-0.01
Sugar	0.14	-0.04	0.14	-0.12	-0.09	0.05
Soft drinks	-0.15	0.04	0.14	-0.08	-0.07	0.04
Egg	0.06	0.03	0.21	0.01	-0.04	0.02
Cheese	-0.08	0.00	0.16	0.26	-0.03	0.01
Mixed dishes	0.01	-0.04	0.37	0.21	-0.01	0.08
Red meat	-0.07	0.04	0.65	0.11	-0.07	0.04
Game	-0.08	0.04	0.16	-0.04	0.12	-0.03
Cured/processed Red meat	0.06	0.34	0.63	-0.07	0.01	0.04
Cured/processed meat	0.02	0.98	0.21	-0.08	-0.01	0.02
Poultry	0.02	0.16	-0.07	0.20	0.01	-0.03
FISH	0.00	0.75	-0.29	0.16	0.02	0.00
Processed fish	-0.01	0.58	-0.13	0.13	0.03	0.04
Fruit Juice	0.16	-0.05	0.08	0.18	0.05	0.08
Other fruit	-0.02	-0.01	0.02	-0.02	0.84	-0.01
Root Vegetables	0.10	0.03	0.27	0.13	-0.03	0.04
Cruciferous Vegetables	0.01	0.02	0.00	0.55	0.08	-0.02
Other Greens	-0.10	0.02	-0.10	0.63	0.07	-0.04
Beans, Peas	0.13	0.00	0.13	0.42	-0.02	0.05
Tomato Sauce	0.01	-0.01	0.09	0.58	0.01	0.03
Other Vegetables	0.03	0.00	0.13	0.60	-0.01	-0.04
Total cereals and grains	0.23	-0.05	0.18	0.22	0.15	0.06
Whole grains	0.12	0.00	-0.09	0.29	0.03	-0.05
Desserts and sweets	0.00	0.00	-0.01	0.00	0.00	1.13
Vegetable juice	0.01	-0.03	0.06	0.24	-0.04	-0.02
Beer	-0.18	0.06	0.12	-0.03	-0.07	-0.03
White Wine	-0.18	-0.03	0.09	0.16	-0.09	-0.02
Red wine	-0.13	0.03	-0.01	0.06	-0.04	-0.01
Liquor	-0.07	0.04	0.05	0.00	-0.09	-0.03
Citrus	0.08	0.01	0.00	0.11	0.29	0.00
Berries	-0.02	0.04	-0.04	0.05	0.60	0.03
Dried Fruit	0.06	-0.05	0.02	0.02	0.50	0.01
Canned Fruit	0.19	-0.04	0.08	0.10	0.06	0.10
Pies, Tarts	-0.01	-0.02	0.00	-0.02	0.01	0.56

Jam, Jelly	0.24	-0.01	0.01	-0.02	0.06	0.11
Pickled Vegetables	0.14	0.02	0.08	0.19	0.04	0.06

Table 5.6.3 Odds ratios and 95% CI in multivariate logistical regression of the NOCS (Newfoundland)

Covariates	OR[a]	95% CI
Socioeconomic status	0.89	(0.82, 0.96)
Processed meat	1.08	(1.04, 1.12)
Prudent vegetables	0.93	(0.88, 0.97)
Fruit	1.00	(0.95, 1.05)
Sex (female VS male)	1.25	(0.93, 1.67)
Age	1.03	(1.02, 1.05)
Screen (no VS yes)	2.67	(1.83, 3.91)
Inflammatory bowel disease	0.93	(0.38, 2.26)
NSAID	1.38	(1.04, 1.83)
Physical activity	1.00	(1.00, 1.00)
Smoking (former VS never)	1.44	(1.05, 1.97)
Smoking (former VS never)	1.85	(1.23, 2.79)
BMI	1.02	(0.99, 1.05)
Family history score of CRC	1.06	(1.04, 1.08)

a: adjusted for Socioeconomic status, Processed meat, Prudent vegetables, Fruit, Sex, Age, Screen, Inflammatory bowel disease, NSAID, Physical activity, Smoking, BMI, Family history score of CRC

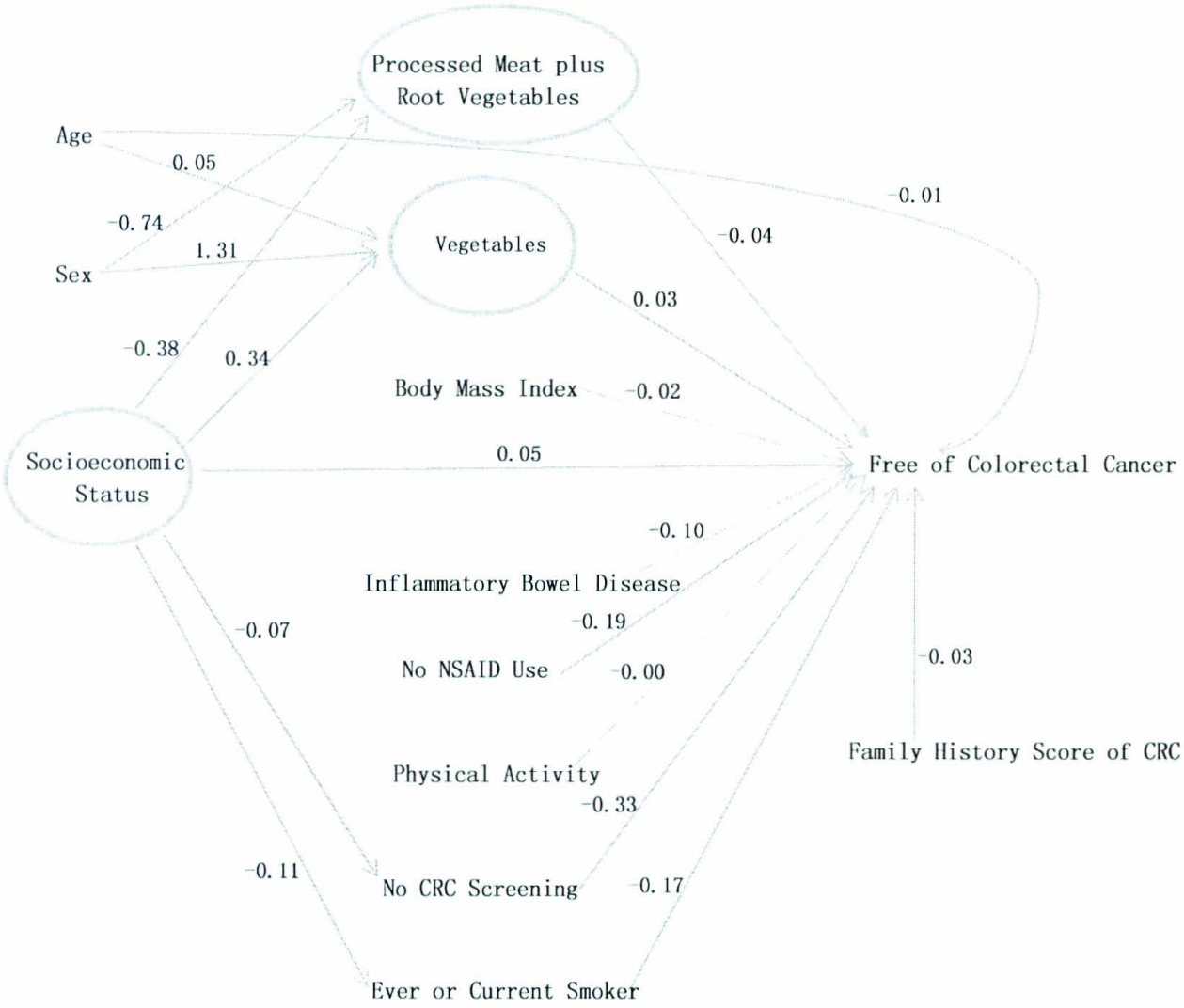


Figure 5.6.2 Conceptualized structural equation model of the etiology of colorectal cancer
*: solid lines represented significant path coefficients ($P \leq 0.05$) while dotted lines indicated insignificant path coefficients ($P \geq 0.05$).

Chapter 6 Summary

The two projects included in this thesis mainly explored how physical activity, socioeconomic status and some common candidate risk factors were linked to the development of colorectal cancer. Engaging in physical activity has long been considered as an effective strategy for cancer prevention [12]. Walking is one of the most common forms of moderate level physical activity among middle-aged and older people [195]. Its impact on CRC risk has only been examined by a few studies [196-198]. The potential benefits of moderate intensity physical activity, particularly the specific role of walking in cancer prevention, are unclear. Results from this study showed that the highest quintile of walking was associated with increased colorectal cancer risk for both males and females in both provinces (highest VS lowest: ON: OR=1.51, 95%CI=1.07-2.13; NL: OR=2.01, 95%CI=1.25-3.22; pooled analysis: OR=1.70, 95%CI=1.09-2.66). However, this result could be biased because a higher proportion of cases respond to the walking item in PHQ than controls. In addition, walking is only a part of total recreational physical activity. Therefore, walking did not appear to be an effective strategy for colorectal cancer prevention in this study.

Non-walking exercise was not significantly associated with reduced risk of colorectal cancer for both sexes and provinces. These findings suggested that increasing amounts of non-walking exercise could reduce the risk of colorectal cancer. Occupational physical activity was not included in the analysis because the data regarding occupational physical activity was not available for this analysis. However, education levels and incomes could explain a proportion of the variation associated with occupation. Future prospective studies in large populations on physical activity are needed to evaluate effective frequency, duration and

intensity of physical activity in relation to colon and rectal cancer prevention.

Dietary factors [96, 124, 142, 219], physical inactivity [15, 17, 18, 150, 152, 220], smoking [158], alcohol consumption [161, 222, 223], smoking [205, 221] and socioeconomic status [224] have been linked to the development of CRC. Existing epidemiologic studies have not studied how risk factors work together to increase the incidence of CRC so the true effect of each factor could be under- or over- estimated. The second component of this thesis was to explore how SES directly influences the risk of developing CRC and its mediated effect on CRC risk through diet while adjusting for possible risk factors of alcohol intake, smoking, physical inactivity, and obesity.

Identifying major dietary patterns through exploratory factor analysis, a relatively new approach in epidemiology, has allowed us to investigate the interrelations of multiple food items or nutrients simultaneously, which has overcome the limitation of partially examining dietary risk factors [225]. In this study, exploratory factor analysis was used to identify dietary patterns measured by the 39 food groups. Then, the direct and intermediate effects of risk factors were examined using structural equation modeling. The results from multivariate regression analysis indicated that age (OR=1.03), SES (OR=0.89), processed meat intake (OR=1.08), no CRC screening (OR=2.67), smoking (OR=1.44, 1.85 (ever, current)), and family history score of CRC (OR=1.06), were significantly associated with the risk of CRC. In addition to the direct effect of SES (β=0.05) on the risk of CRC, the indirect effect (β=0.06) of SES on the risk of CRC also appeared to exist through processed meat intake (β=0.01), lower vegetables intake (β=0.01), less likely to have CRC screening (β=0.02), and smoking (β=0.02). This study suggested that the NL population has three major dietary patterns: (1) processed meat plus root vegetables; (2) vegetables; and (3) fruits. In addition, structural

equation modeling used in this study, a relatively new approach in epidemiological studies, provided unique information of the direct effect of socioeconomic status on the development of CRC and its indirect effects through a set of candidate CRC risk factors.

This study only presented one 'corner' of the much larger "web" of associations in cancer etiology. It is possible that a more comprehensive model could explain data better than our suggested model. Future research in this area should focus on investigating the interrelations of obesity, physical inactivity, history of cancer related diseases, medication use and other candidate risk factors of developing cancer.

References

1. Widaman, K.F. and J.S. Thompson, *On specifying the null model for incremental fit indices in structural equation modeling.* Psychological methods, 2003. **8**(1): p. 16-37.
2. Hu, L.T. and P.M. Bentler, *Fit indices in covariance structure modeling: Sensitivity to underparameterized model misspecification.* Psychological methods, 1998. **3**(4): p. 424-453.
3. *Path Analysis*. 2012 [cited 2012 03-31]; Available from: http://people.eku.edu/falkenbergs/psy862/pathdefs.htm.
4. Alder, L. and W.R. Lindsay, *Exploratory factor analysis and convergent validity of the Dundee Provocation Inventory.* Journal of intellectual & developmental disability, 2007. **32**(3): p. 190-9.
5. Abdullah, F., *"HEdPERF versus SERVPERF: The quest for ideal measuring instrument of service quality in higher education sector"*, in *Quality Assurance in Education*2005. p. 305-328.
6. Bentler, P.M. and D.G. Bonett, *Significance tests and goodness of fit in the analysis of covariance structures.* . Psychological Bulletin, 1980. **88**(3): p. 588-606.
7. Schutte, M., S. Sandrock, and B. Griefahn, *Factorial validity of the noise sensitivity questionnaire.* Noise & health, 2007. **9**(37): p. 96-100.
8. Rabe-Hesketh, S. and A. Skrondal, *Classical latent variable models for medical research.* Statistical methods in medical research, 2008. **17**(1): p. 5-32.
9. Baranowski, T., C. Anderson, and C. Carmack, *Mediating variable framework in physical activity interventions. How are we doing? How might we do better?* American journal of preventive medicine, 1998. **15**(4): p. 266-97.
10. Bollen, K.A., *Structural Equation Models*. 2005.
11. CCS, *Canadian cancer statistics 2010*, C.C. Society, Editor 2010: Toronto, Canada. p. 13-15.
12. Chao, A., et al., *Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort.* Cancer Epidemiol Biomarkers Prev, 2004. **13**(12): p. 2187-95.
13. Spence, R.R., K.C. Heesch, and W.J. Brown, *A systematic review of the association between physical activity and colorectal cancer risk.* Scand J Med Sci Sports, 2009.
14. Samad, A.K., et al., *A meta-analysis of the association of physical activity with reduced risk of colorectal cancer.* Colorectal Dis, 2005. **7**(3): p. 204-13.
15. Colditz, G.A., C.C. Cannuscio, and A.L. Frazier, *Physical activity and reduced risk of colon cancer: implications for prevention.* Cancer Causes Control, 1997. **8**(4): p. 649-67.
16. Research., W.C.R.F.A.I.f.C., *Food, nutriiton, and physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR,2007.*
17. Colbert, L.H., et al., *Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(3): p. 265-8.
18. Giovannucci, E., et al., *Physical activity, obesity, and risk for colon cancer and adenoma in men.* Ann Intern Med, 1995. **122**(5): p. 327-34.
19. Nilsen, T.I. and L.J. Vatten, *Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis.* Br J Cancer, 2001. **84**(3): p. 417-22.
20. Thun, M.J., et al., *Risk factors for fatal colon cancer in a large prospective study.* J Natl Cancer Inst, 1992. **84**(19): p. 1491-500.
21. Longnecker, M.P., et al., *A case-control study of physical activity in relation to risk of cancer of the right colon and rectum in men.* Int J Epidemiol, 1995. **24**(1): p. 42-50.
22. Steindorf, K., et al., *Combined risk assessment of physical activity and dietary habits on the development of colorectal cancer. A hospital-based case-control study in Poland.* Eur J Cancer Prev, 2000. **9**(5): p. 309-16.
23. Lee, I.M., R.S. Paffenbarger, Jr., and C. Hsieh, *Physical activity and risk of developing colorectal cancer among college alumni.* J Natl Cancer Inst, 1991. **83**(18): p. 1324-9.
24. Thune, I. and E. Lund, *Physical activity and risk of colorectal cancer in men and women.* Br J Cancer, 1996. **73**(9): p. 1134-40.
25. Wannamethee, S.G., A.G. Shaper, and M. Walker, *Physical activity and risk of cancer in middle-aged men.* Br J Cancer, 2001. **85**(9): p. 1311-6.
26. Slattery, M.L., *Physical activity and colorectal cancer.* Sports Med, 2004. **34**(4): p. 239-52.
27. Ahmed, F.E., *Effect of diet, life style, and other environmental/chemopreventive factors on colorectal cancer development, and assessment of the risks.* J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 2004. **22**(2): p. 91-147.
28. Akhter, M., et al., *Cigarette smoking and the risk of colorectal cancer among men: a prospective study in Japan.* Eur J Cancer Prev, 2007. **16**(2): p. 102-7.

29. Alberts, D.S., et al., *Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network.* N Engl J Med, 2000. **342**(16): p. 1156-62.
30. Alcorn, J.M., *Colorectal cancer prevention: a primary care approach.* Geriatrics, 1992. **47**(2): p. 24-30.
31. Campbell, P.T., *Excess body weight, exogenous hormones, and polymorphisms in steroid metabolism: links with hereditary colorectal cancer*, in *Department of Public Health Sciences*2007, University of Toronto.
32. Chan, A.T. and E.L. Giovannucci, *Primary prevention of colorectal cancer.* Gastroenterology, 2010. **138**(6): p. 2029-2043 e10.
33. Chao, A., et al., *Meat consumption and risk of colorectal cancer.* JAMA, 2005. **293**(2): p. 172-82.
34. Chao, A., et al., *Cigarette smoking and colorectal cancer mortality in the cancer prevention study II.* J Natl Cancer Inst, 2000. **92**(23): p. 1888-96.
35. Chiu, B.C., et al., *Dietary factors and risk of colon cancer in Shanghai, China.* Cancer Epidemiol Biomarkers Prev, 2003. **12**(3): p. 201-8.
36. Cutler, G.J., et al., *Major patterns of dietary intake in adolescents and their stability over time.* J Nutr, 2009. **139**(2): p. 323-8.
37. Campbell, P.T., et al., *Mismatch repair polymorphisms and risk of colon cancer, tumour microsatellite instability and interactions with lifestyle factors.* Gut, 2009. **58**(5): p. 661-7.
38. Anderson, N.B. and C.A. Armstead, *Toward understanding the association of socioeconomic status and health: a new challenge for the biopsychosocial approach.* Psychosom Med, 1995. **57**(3): p. 213-25.
39. Chen, K., et al., *Twenty-year secular changes in sex specific lung cancer incidence rates in an urban Chinese population.* Lung Cancer, 2006. **51**(1): p. 13-9.
40. Hair, F., *Structural Equation Modeling. In: Multivariate data analysis with readings*1998, Englewood Cliffs, N.J: Prentice Hall.
41. Wilkinson, R. and M. Marmot, *Social Determinants of Health*, in *The Solid Facts*2003, World Health Organization: Copenhagen, Denmark.
42. Gomez, S.L., et al., *Longitudinal, population-based study of racial/ethnic differences in colorectal cancer survival: impact of neighborhood socioeconomic status, treatment and comorbidity.* BMC Cancer, 2007. **7**: p. 193.
43. Bao, Y., S.A. Fox, and J.J. Escarce, *Socioeconomic and racial/ethnic differences in the discussion of cancer screening: "between-" versus "within-" physician differences.* Health Serv Res, 2007. **42**(3 Pt 1): p. 950-70.
44. *National Cancer Institute: Colon and Rectal Cancer* 2011 [cited 2011 May 23rd]; Available from: http://www.cancer.gov/cancertopics/types/colon-and-rectal.
45. *National Cancer Institute: The Colon and Rectum.* 2011 [cited 2011 May 23rd]; Available from: http://www.cancer.gov/cancertopics/wyntk/colon-and-rectal/page2.
46. Markowitz, S., *DNA repair defects inactivate tumor suppressor genes and induce hereditary and sporadic colon cancers.* J Clin Oncol, 2000. **18**(21 Suppl): p. 75S-80S.
47. WHO. *World Health Organization: Cancer.* 2011 [cited 2011 May 22nd]; Available from: http://www.who.int/cancer/en/.
48. IARC. *International Agency for Research on Cancer GLOBOCAN 2008.* 2011 [cited 2011 May 24th]; Available from: http://globocan.iarc.fr/factsheets/cancers/colorectal.asp.
49. *IARC handbooks of cancer prevention*, in *Fruit IARC, vegetables* H. Vainio and F. Bianchini, Editors. 2003: Lyon (France).
50. Green, R.C., et al., *Very high incidence of familial colorectal cancer in Newfoundland: a comparison with Ontario and 13 other population-based studies.* Fam Cancer, 2007. **6**(1): p. 53-62.
51. Amersi, F., M. Agustin, and C.Y. Ko, *Colorectal cancer: epidemiology, risk factors, and health services.* Clin Colon Rectal Surg, 2005. **18**(3): p. 133-40.
52. Heavey, P.M., D. McKenna, and I.R. Rowland, *Colorectal cancer and the relationship between genes and the environment.* Nutr Cancer, 2004. **48**(2): p. 124-41.
53. Potter, J. and D. Hunt, *Colorectal cancer* 2nd ed. Monographs in epidemiology and biostatistics, ed. H.-O. Adami, D. Hunter, and D. Trichopoulos2008, New York: Oxford University Press. 748.
54. Ahmed, F.E., *Gene-gene, gene-environment & multiple interactions in colorectal cancer.* J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 2006. **24**(1): p. 1-101.
55. Boyle, P. and M.E. Leon, *Epidemiology of colorectal cancer.* Br Med Bull, 2002. **64**: p. 1-25.
56. WCRF and AICR, *World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, 2007, AICR Washington DC

57. Gryfe, R., *Inherited colorectal cancer syndromes.* Clin Colon Rectal Surg, 2009. **22**(4): p. 198-208.
58. Jeter, J.M., W. Kohlmann, and S.B. Gruber, *Genetics of colorectal cancer.* Oncology (Williston Park), 2006. **20**(3): p. 269-76; discussion 285-6, 288-9.
59. Bulow, S., et al., *The incidence rate of familial adenomatous polyposis. Results from the Danish Polyposis Register.* Int J Colorectal Dis, 1996. **11**(2): p. 88-91.
60. de la Chapelle, A., *The incidence of Lynch syndrome.* Fam Cancer, 2005. **4**(3): p. 233-7.
61. Bonk, T., et al., *Molecular diagnosis of familial adenomatous polyposis (FAP): genotyping of adenomatous polyposis coli (APC) alleles by MALDI-TOF mass spectrometry.* Clin Biochem, 2002. **35**(2): p. 87-92.
62. Powell, S.M., et al., *Molecular diagnosis of familial adenomatous polyposis.* N Engl J Med, 1993. **329**(27): p. 1982-7.
63. Haenszel, W., et al., *Large-bowel cancer in Hawaiian Japanese.* J Natl Cancer Inst, 1973. **51**(6): p. 1765-79.
64. McMichael, A.J., et al., *Patterns of gastro-intestinal cancer in European migrants to Australia: the role of dietary change.* Int J Cancer, 1980. **25**(4): p. 431-7.
65. Nasca, P.C., et al., *Cancer among the foreign-born in New York State.* Cancer, 1981. **48**(10): p. 2323-8.
66. WHO. *World Health Organization: Cancer mortality and morbidity.* 2011 [cited 2011 May 23rd]; Available from: http://www.who.int/gho/ncd/mortality_morbidity/cancer_text/en/.
67. Tavani, A., et al., *Education, socioeconomic status and risk of cancer of the colon and rectum.* Int J Epidemiol, 1999. **28**(3): p. 380-5.
68. Ferraroni, M., et al., *Socioeconomic indicators, tobacco and alcohol in the aetiology of digestive tract neoplasms.* Int J Epidemiol, 1989. **18**(3): p. 556-62.
69. Doll, R. and R. Peto, *The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today.* J Natl Cancer Inst, 1981. **66**(6): p. 1191-308.
70. Giovannucci, E., et al., *Relationship of diet to risk of colorectal adenoma in men.* J Natl Cancer Inst, 1992. **84**(2): p. 91-8.
71. Huxley, R.R., et al., *The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence.* Int J Cancer, 2009. **125**(1): p. 171-80.
72. Liang, P.S., T.Y. Chen, and E. Giovannucci, *Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis.* Int J Cancer, 2009. **124**(10): p. 2406-15.
73. Platz, E.A., et al., *Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men.* Cancer Causes Control, 2000. **11**(7): p. 579-88.
74. Giovannucci, E., et al., *Physical activity, obesity, and risk of colorectal adenoma in women (United States).* Cancer Causes Control, 1996. **7**(2): p. 253-63.
75. *World Cancer Research Fund. Food, Nutrition, and the Prevention of Cancer: a Global Perspective. .* Washington, DC: Ameircan Institute for Cancer Research, 1997(
).
76. West, D.W., et al., *Dietary intake and colon cancer: sex- and anatomic site-specific associations.* Am J Epidemiol, 1989. **130**(5): p. 883-94.
77. Slattery, M.L., et al., *Dietary energy sources and colon cancer risk.* Am J Epidemiol, 1997. **145**(3): p. 199-210.
78. Satia-Abouta, J., et al., *Associations of total energy and macronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina colon cancer study.* Am J Epidemiol, 2003. **158**(10): p. 951-62.
79. Giovannucci, E., et al., *Intake of fat, meat, and fiber in relation to risk of colon cancer in men.* Cancer Res, 1994. **54**(9): p. 2390-7.
80. Franceschi, S., et al., *Dietary glycemic load and colorectal cancer risk.* Ann Oncol, 2001. **12**(2): p. 173-8.
81. Bruce, W.R., A. Giacca, and A. Medline, *Possible mechanisms relating diet and risk of colon cancer.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(12): p. 1271-9.
82. Bruce, W.R., T.M. Wolever, and A. Giacca, *Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance.* Nutr Cancer, 2000. **37**(1): p. 19-26.
83. Larsson, S.C., N. Orsini, and A. Wolk, *Diabetes mellitus and risk of colorectal cancer: a meta-analysis.* J Natl Cancer Inst, 2005. **97**(22): p. 1679-87.
84. Hu, F.B., et al., *Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women.* J Natl Cancer Inst, 1999. **91**(6): p. 542-7.
85. Yang, Y.X., S. Hennessy, and J.D. Lewis, *Type 2 diabetes mellitus and the risk of colorectal cancer.* Clin Gastroenterol Hepatol, 2005. **3**(6): p. 587-94.
86. Limburg, P.J., et al., *Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: a population-based, retrospective cohort study.* Am J Gastroenterol, 2006. **101**(8): p. 1872-9.

87. Limburg, P.J., et al., *Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women's Health Study.* Cancer Epidemiol Biomarkers Prev, 2005. **14**(1): p. 133-7.
88. WCRF and AICR, *World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a Global Perspective*, 1997, American Institute for Cancer Research: Washington (DC).
89. Kritchevsky, D., *Epidemiology of fibre, resistant starch and colorectal cancer.* Eur J Cancer Prev, 1995. **4**(5): p. 345-52.
90. Burkitt, D.P., *Epidemiology of cancer of the colon and rectum.* Cancer, 1971. **28**(1): p. 3-13.
91. Sugimura, T., et al., *Heterocyclic amines: Mutagens/carcinogens produced during cooking of meat and fish.* Cancer Sci, 2004. **95**(4): p. 290-9.
92. Kazerouni, N., et al., *Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study.* Food Chem Toxicol, 2001. **39**(5): p. 423-36.
93. Hughes, R., et al., *Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation.* Carcinogenesis, 2001. **22**(1): p. 199-202.
94. Huang, X., *Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal.* Mutat Res, 2003. **533**(1-2): p. 153-71.
95. Giovannucci, E. and W.C. Willett, *Dietary factors and risk of colon cancer.* Ann Med, 1994. **26**(6): p. 443-52.
96. Bostick, R.M., et al., *Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States).* Cancer Causes Control, 1994. **5**(1): p. 38-52.
97. MacLean, C.H., et al., *Effects of omega-3 fatty acids on cancer risk: a systematic review.* JAMA, 2006. **295**(4): p. 403-15.
98. Norat, T., et al., *Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition.* J Natl Cancer Inst, 2005. **97**(12): p. 906-16.
99. Geelen, A., et al., *Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies.* Am J Epidemiol, 2007. **166**(10): p. 1116-25.
100. Hall, M.N., et al., *Blood levels of long-chain polyunsaturated fatty acids, aspirin, and the risk of colorectal cancer.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(2): p. 314-21.
101. Hall, M.N., et al., *A 22-year prospective study of fish, n-3 fatty acid intake, and colorectal cancer risk in men.* Cancer Epidemiol Biomarkers Prev, 2008. **17**(5): p. 1136-43.
102. Lopez-Garcia, E., et al., *Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women.* J Nutr, 2004. **134**(7): p. 1806-11.
103. Rao, C.V., et al., *Modulation of experimental colon tumorigenesis by types and amounts of dietary fatty acids.* Cancer Res, 2001. **61**(5): p. 1927-33.
104. Collett, E.D., et al., *n-6 and n-3 polyunsaturated fatty acids differentially modulate oncogenic Ras activation in colonocytes.* Am J Physiol Cell Physiol, 2001. **280**(5): p. C1066-75.
105. Daniel, C.R., et al., *Dietary intake of omega-6 and omega-3 fatty acids and risk of colorectal cancer in a prospective cohort of U.S. men and women.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(2): p. 516-25.
106. Levi, F., et al., *Macronutrients and colorectal cancer: a Swiss case-control study.* Ann Oncol, 2002. **13**(3): p. 369-73.
107. Franceschi, S., et al., *Macronutrient intake and risk of colorectal cancer in Italy.* Int J Cancer, 1998. **76**(3): p. 321-4.
108. Beresford, S.A., et al., *Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial.* JAMA, 2006. **295**(6): p. 643-54.
109. Benito, E., et al., *Diet and colorectal adenomas: a case-control study in Majorca.* Int J Cancer, 1993. **55**(2): p. 213-9.
110. Potter, J.D., et al., *Colon cancer: a review of the epidemiology.* Epidemiol Rev, 1993. **15**(2): p. 499-545.
111. Giovannucci, E., et al., *Folate, methionine, and alcohol intake and risk of colorectal adenoma.* J Natl Cancer Inst, 1993. **85**(11): p. 875-84.
112. Nelson, R.L., et al., *Body iron stores and risk of colonic neoplasia.* J Natl Cancer Inst, 1994. **86**(6): p. 455-60.
113. Newmark, H.L., M.J. Wargovich, and W.R. Bruce, *Colon cancer and dietary fat, phosphate, and calcium: a hypothesis.* J Natl Cancer Inst, 1984. **72**(6): p. 1323-5.
114. Pence, B.C., *Role of calcium in colon cancer prevention: experimental and clinical studies.* Mutat Res, 1993. **290**(1): p. 87-95.
115. Peters, U., et al., *Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(12): p. 1267-74.
116. Fedirko, V., et al., *Effects of vitamin d and calcium on proliferation and differentiation in normal colon*

mucosa: a randomized clinical trial. Cancer Epidemiol Biomarkers Prev, 2009. **18**(11): p. 2933-41.
117. Fedirko, V., et al., *Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial.* Cancer Prev Res (Phila), 2009. **2**(3): p. 213-23.
118. Ehrlich, M., *DNA methylation in cancer: too much, but also too little.* Oncogene, 2002. **21**(35): p. 5400-13.
119. Glynn, S.A., et al., *Colorectal cancer and folate status: a nested case-control study among male smokers.* Cancer Epidemiol Biomarkers Prev, 1996. **5**(7): p. 487-94.
120. Giovannucci, E., *Epidemiologic studies of folate and colorectal neoplasia: a review.* J Nutr, 2002. **132**(8 Suppl): p. 2350S-2355S.
121. Bird, C.L., et al., *Red cell and plasma folate, folate consumption, and the risk of colorectal adenomatous polyps.* Cancer Epidemiol Biomarkers Prev, 1995. **4**(7): p. 709-14.
122. Tseng, M., et al., *Micronutrients and the risk of colorectal adenomas.* Am J Epidemiol, 1996. **144**(11): p. 1005-14.
123. Sanjoaquin, M.A., et al., *Folate intake and colorectal cancer risk: a meta-analytical approach.* Int J Cancer, 2005. **113**(5): p. 825-8.
124. Bjelakovic, G., et al., *Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis.* Lancet, 2004. **364**(9441): p. 1219-28.
125. Greenberg, E.R., et al., *A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group.* N Engl J Med, 1994. **331**(3): p. 141-7.
126. Connelly-Frost, A., et al., *Selenium, apoptosis, and colorectal adenomas.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(3): p. 486-93.
127. Papaioannou, D., et al., *Antioxidants in the chemoprevention of colorectal cancer and colorectal adenomas in the general population: a systematic review and meta-analysis.* Colorectal Dis, 2010.
128. Martinez, M.E., *Primary prevention of colorectal cancer: lifestyle, nutrition, exercise.* Recent Results Cancer Res, 2005. **166**: p. 177-211.
129. Truswell, A.S., *Meat consumption and cancer of the large bowel.* Eur J Clin Nutr, 2002. **56 Suppl 1**: p. S19-24.
130. Sandhu, M.S., I.R. White, and K. McPherson, *Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(5): p. 439-46.
131. Truswell, A.S., *Report of an expert workshop on meat intake and colorectal cancer risk convened in December 1998 in Adelaide, South Australia.* Eur J Cancer Prev, 1999. **8**(3): p. 175-8.
132. Morotomi, M., et al., *Effects of a high-fat diet on azoxymethane-induced aberrant crypt foci and fecal biochemistry and microbial activity in rats.* Nutr Cancer, 1997. **27**(1): p. 84-91.
133. Howe, G.R., et al., *The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies.* Cancer Causes Control, 1997. **8**(2): p. 215-28.
134. Gaard, M., S. Tretli, and E.B. Loken, *Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women.* Eur J Cancer Prev, 1996. **5**(6): p. 445-54.
135. Levi, F., et al., *Dietary fibre and the risk of colorectal cancer.* Eur J Cancer, 2001. **37**(16): p. 2091-6.
136. Terry, P., et al., *Fruit, vegetables, dietary fiber, and risk of colorectal cancer.* J Natl Cancer Inst, 2001. **93**(7): p. 525-33.
137. Fuchs, C.S., et al., *Dietary fiber and the risk of colorectal cancer and adenoma in women.* N Engl J Med, 1999. **340**(3): p. 169-76.
138. Wasan, H.S., et al., *Dietary fat influences on polyp phenotype in multiple intestinal neoplasia mice.* Proc Natl Acad Sci U S A, 1997. **94**(7): p. 3308-13.
139. Slattery, M.L., *Analysis of dietary patterns in epidemiological research.* Appl Physiol Nutr Metab, 2010. **35**(2): p. 207-10.
140. Slattery, M.L., *Defining dietary consumption: is the sum greater than its parts?* Am J Clin Nutr, 2008. **88**(1): p. 14-5.
141. Dixon, L.B., et al., *Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project.* Am J Clin Nutr, 2004. **80**(4): p. 1003-11.
142. Bravi, F., et al., *Nutrient dietary patterns and the risk of colorectal cancer: a case-control study from Italy.* Cancer Causes Control, 2010. **21**(11): p. 1911-8.
143. Cottet, V., et al., *Dietary patterns and the risk of colorectal adenoma recurrence in a European intervention trial.* Eur J Cancer Prev, 2005. **14**(1): p. 21-9.
144. Fung, T., et al., *Major dietary patterns and the risk of colorectal cancer in women.* Arch Intern Med, 2003. **163**(3): p. 309-14.
145. Terry, P., et al., *Prospective study of major dietary patterns and colorectal cancer risk in women.* Am J Epidemiol, 2001. **154**(12): p. 1143-9.

146. Kim, M.K., et al., *Dietary patterns and subsequent colorectal cancer risk by subsite: a prospective cohort study.* Int J Cancer, 2005. **115**(5): p. 790-8.
147. Kurotani, K., et al., *Dietary patterns and colorectal cancer in a Japanese population: the Fukuoka Colorectal Cancer Study.* Br J Nutr, 2010. **104**(11): p. 1703-11.
148. Randall, E., et al., *Dietary patterns and colon cancer in western New York.* Nutr Cancer, 1992. **18**(3): p. 265-76.
149. WHO. *World Health Organization: New physical activity guidance can help reduce risk of breast, colon cancers.* 2011 [cited 2011 May 23rd]; Available from: http://www.who.int/mediacentre/news/notes/2011/world_cancer_day_20110204/en/.
150. Gerhardsson de Verdier, M., et al., *Physical activity and colon cancer: a case-referent study in Stockholm.* Int J Cancer, 1990. **46**(6): p. 985-9.
151. Lee, I.M., et al., *Physical activity and risk of colon cancer: the Physicians' Health Study (United States).* Cancer Causes Control, 1997. **8**(4): p. 568-74.
152. Friedenreich, C., et al., *Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(12): p. 2398-407.
153. Schnohr, P., et al., *Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 Danish men and women.* Scand J Public Health, 2005. **33**(4): p. 244-9.
154. *World Cancer Research Fund/American institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective*, 2007: Washington DC p. 280.
155. Slattery, M.L., et al., *Energy balance and colon cancer--beyond physical activity.* Cancer Res, 1997. **57**(1): p. 75-80.
156. Giovannucci, E., *An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(7): p. 725-31.
157. Tsoi, K.K., et al., *Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies.* Clin Gastroenterol Hepatol, 2009. **7**(6): p. 682-688 e1-5.
158. Botteri, E., et al., *Smoking and colorectal cancer: a meta-analysis.* JAMA, 2008. **300**(23): p. 2765-78.
159. Limburg, P.J., et al., *Cigarette smoking and colorectal cancer: long-term, subsite-specific risks in a cohort study of postmenopausal women.* Clin Gastroenterol Hepatol, 2003. **1**(3): p. 202-10.
160. Kune, G.A. and L. Vitetta, *Alcohol consumption and the etiology of colorectal cancer: a review of the scientific evidence from 1957 to 1991.* Nutr Cancer, 1992. **18**(2): p. 97-111.
161. Choi, S.W., et al., *Chronic alcohol consumption induces genomic but not p53-specific DNA hypomethylation in rat colon.* J Nutr, 1999. **129**(11): p. 1945-50.
162. Ning, Y., L. Wang, and E.L. Giovannucci, *A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies.* Obes Rev, 2010. **11**(1): p. 19-30.
163. Giovannucci, E., *Insulin and colon cancer.* Cancer Causes Control, 1995. **6**(2): p. 164-79.
164. Gunter, M.J. and M.F. Leitzmann, *Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes.* J Nutr Biochem, 2006. **17**(3): p. 145-56.
165. John, B.J., et al., *Systematic review: adipose tissue, obesity and gastrointestinal diseases.* Aliment Pharmacol Ther, 2006. **23**(11): p. 1511-23.
166. Stattin, P., et al., *Obesity and colon cancer: does leptin provide a link?* Int J Cancer, 2004. **109**(1): p. 149-52.
167. Shoelson, S.E., L. Herrero, and A. Naaz, *Obesity, inflammation, and insulin resistance.* Gastroenterology, 2007. **132**(6): p. 2169-80.
168. Kim, S., et al., *Circulating levels of inflammatory cytokines and risk of colorectal adenomas.* Cancer Res, 2008. **68**(1): p. 323-8.
169. Hotamisligil, G.S., *Inflammation and metabolic disorders.* Nature, 2006. **444**(7121): p. 860-7.
170. Slattery, M.L., et al., *Aspirin, NSAIDs, and colorectal cancer: possible involvement in an insulin-related pathway.* Cancer Epidemiol Biomarkers Prev, 2004. **13**(4): p. 538-45.
171. Baron, J.A., et al., *A randomized trial of aspirin to prevent colorectal adenomas.* N Engl J Med, 2003. **348**(10): p. 891-9.
172. Giovannucci, E., et al., *Aspirin and the risk of colorectal cancer in women.* N Engl J Med, 1995. **333**(10): p. 609-14.
173. Steinbach, G., et al., *The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis.* N Engl J Med, 2000. **342**(26): p. 1946-52.
174. Kopp, E. and S. Ghosh, *Inhibition of NF-kappa B by sodium salicylate and aspirin.* Science, 1994. **265**(5174): p. 956-9.
175. Schwenger, P., et al., *Sodium salicylate induces apoptosis via p38 mitogen-activated protein kinase but inhibits tumor necrosis factor-induced c-Jun N-terminal kinase/stress-activated protein kinase activation.* Proc Natl Acad Sci U S A, 1997. **94**(7): p. 2869-73.
176. Martinez, M.E., et al., *Pronounced reduction in adenoma recurrence associated with aspirin use and a*

polymorphism in the ornithine decarboxylase gene. Proc Natl Acad Sci U S A, 2003. **100**(13): p. 7859-64.
177. Cotterchio, M., et al., *Ontario familial colon cancer registry: methods and first-year response rates.* Chronic Dis Can, 2000. **21**(2): p. 81-6.
178. Cotterchio, M., et al., *Colorectal screening is associated with reduced colorectal cancer risk: a case-control study within the population-based Ontario Familial Colorectal Cancer Registry.* Cancer Causes Control, 2005. **16**(7): p. 865-75.
179. Campbell, P.T., et al., *Excess body weight and colorectal cancer risk in Canada: associations in subgroups of clinically defined familial risk of cancer.* Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2007. **16**(9): p. 1735-44.
180. Squires, J., et al., *Pickled meat consumption and colorectal cancer (CRC): a case-control study in Newfoundland and Labrador, Canada.* Cancer Causes Control, 2010. **21**(9): p. 1513-21.
181. Sun, Z., et al., *Calcium and vitamin D and risk of colorectal cancer: results from a large population-based case-control study in Newfoundland and Labrador and Ontario.* Canadian journal of public health. Revue canadienne de sante publique, 2011. **102**(5): p. 382-9.
182. Wang, P.P., et al., *Validity of random-digit-dialing in recruiting controls in a case-control study.* Am J Health Behav, 2009. **33**(5): p. 513-20.
183. SUN, Z., *Association of dietary intakes with risk of colorectal cancer: results from a population-based case-control study in Newfoundland and Labrador*, in *Division of Community Health and Humanities*2010, Memorial University of Newfoundland: St John's.
184. Kolonel, L.N., et al., *A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics.* Am J Epidemiol, 2000. **151**(4): p. 346-57.
185. Stram, D.O., et al., *Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles.* Am J Epidemiol, 2000. **151**(4): p. 358-70.
186. Ainsworth, B.E., et al., *2011 Compendium of Physical Activities: a second update of codes and MET values.* Medicine and science in sports and exercise, 2011. **43**(8): p. 1575-81.
187. Ainsworth, B.E., et al., *Compendium of physical activities: classification of energy costs of human physical activities.* Medicine and science in sports and exercise, 1993. **25**(1): p. 71-80.
188. Ullman, J.B., *Structural equation modeling: reviewing the basics and moving forward.* J Pers Assess, 2006. **87**(1): p. 35-50.
189. MacCallum, R.C. and J.T. Austin, *Applications of structural equation modeling in psychological research.* Annual Review of Psychology, 2000. **51**: p. 201-226.
190. Le Marchand, L., L.N. Kolonel, and C.N. Yoshizawa, *Lifetime occupational physical activity and prostate cancer risk.* Am J Epidemiol, 1991. **133**(2): p. 103-11.
191. Levi, F., et al., *Occupational and leisure time physical activity and the risk of breast cancer.* Eur J Cancer, 1999. **35**(5): p. 775-8.
192. Slattery, M.L., et al., *Physical activity and colon cancer: a public health perspective.* Ann Epidemiol, 1997. **7**(2): p. 137-45.
193. Tavani, A., et al., *Physical activity and risk of cancers of the colon and rectum: an Italian case-control study.* Br J Cancer, 1999. **79**(11-12): p. 1912-6.
194. White, E., E.J. Jacobs, and J.R. Daling, *Physical activity in relation to colon cancer in middle-aged men and women.* Am J Epidemiol, 1996. **144**(1): p. 42-50.
195. Services, U.D.o.H.a.H., *Chapter 5:Patterns and trends in physical activity. In: physical activity and health: a report of the Surgeon General.*, 1996.
196. Takahashi, H., et al., *Time spent walking and risk of colorectal cancer in Japan: the Miyagi Cohort study.* Eur J Cancer Prev, 2007. **16**(5): p. 403-8.
197. Manson, J.E., et al., *Walking compared with vigorous exercise for the prevention of cardiovascular events in women.* N Engl J Med, 2002. **347**(10): p. 716-25.
198. Wolin, K.Y., et al., *Leisure-time physical activity patterns and risk of colon cancer in women.* Int J Cancer, 2007. **121**(12): p. 2776-81.
199. WHO, *Pacific physical activity guidelines for adults : framework for accelerating the communication of physical activity guidelines*, 2008. p. 9.
200. Pate, R.R., et al., *Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine.* JAMA, 1995. **273**(5): p. 402-7.
201. Services., D.o.H.a.H., *Physical activity and public health: a report of the Surgeon General. Atlanta :Department of Health and Human Services , Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996.*
202. Medicine., A.C.o.S., *Guidelines for exercise testing and prescription. 3rd ed. Philadelphia: Lea & Febiger,1986.*

203. Takahashi, H., et al., *Time spent walking and risk of colorectal cancer in Japan: the Miyagi Cohort study.* European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation, 2007. **16**(5): p. 403-8.
204. Davey Smith, G., et al., *Physical activity and cause-specific mortality in the Whitehall study.* Public Health, 2000. **114**(5): p. 308-15.
205. Zhao, J., et al., *Tobacco smoking and colorectal cancer: a population-based case-control study in Newfoundland and Labrador.* Can J Public Health, 2010. **101**(4): p. 281-9.
206. Slattery, M.L., et al., *Physical activity and colorectal cancer.* Am J Epidemiol, 2003. **158**(3): p. 214-24.
207. Chao, A., et al., *Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort.* Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2004. **13**(12): p. 2187-95.
208. Harriss, D.J., et al., *Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity.* Colorectal Dis, 2009. **11**(7): p. 689-701.
209. Wei, E.K., et al., *Comparison of risk factors for colon and rectal cancer.* Int J Cancer, 2004. **108**(3): p. 433-42.
210. Dukas, L., et al., *Association of bowel movement frequency and use of laxatives with the occurrence of symptomatic gallstone disease in a prospective study of women.* Am J Gastroenterol, 2001. **96**(3): p. 715-21.
211. Giovannucci, E., *Insulin, insulin-like growth factors and colon cancer: a review of the evidence.* J Nutr, 2001. **131**(11 Suppl): p. 3109S-20S.
212. Das, U.N., *Is obesity an inflammatory condition?* Nutrition, 2001. **17**(11-12): p. 953-66.
213. Kohrt, W.M., *Aging and the osteogenic response to mechanical loading.* Int J Sport Nutr Exerc Metab, 2001. **11 Suppl**: p. S137-42.
214. Hak, A.E., et al., *Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women.* Arterioscler Thromb Vasc Biol, 1999. **19**(8): p. 1986-91.
215. Geffken, D.F., et al., *Association between physical activity and markers of inflammation in a healthy elderly population.* Am J Epidemiol, 2001. **153**(3): p. 242-50.
216. Krotkiewski, M., et al., *Effects of physical training on insulin, connecting peptide (C-peptide), gastric inhibitory polypeptide (GIP) and pancreatic polypeptide (PP) levels in obese subjects.* Int J Obes, 1984. **8**(3): p. 193-9.
217. Oktedalen, O., et al., *The effect of physical stress on gastric secretion and pancreatic polypeptide levels in man.* Scand J Gastroenterol, 1984. **19**(6): p. 770-8.
218. WHO and FAO, *Joint WHO/FAO Expert on Diet, Nutrition, and the Prevention of Chronic Disease*, 2003, World Health Organization: Geneva, Switzerland.
219. Bidoli, E., et al., *Food consumption and cancer of the colon and rectum in north-eastern Italy.* Int J Cancer, 1992. **50**(2): p. 223-9.
220. Friedenreich, C.M., *Physical activity and cancer prevention: from observational to intervention research.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(4): p. 287-301.
221. Cleary, S.P., et al., *Cigarette smoking, genetic variants in carcinogen-metabolizing enzymes, and colorectal cancer risk.* Am J Epidemiol, 2010. **172**(9): p. 1000-14.
222. Stolzenberg-Solomon, R.Z., et al., *Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.* Am J Clin Nutr, 2006. **83**(4): p. 895-904.
223. Yamaji, T., et al., *Methionine synthase A2756G polymorphism interacts with alcohol and folate intake to influence the risk of colorectal adenoma.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(1): p. 267-74.
224. Faggiano, F., R. Zanetti, and G. Costa, *Cancer risk and social inequalities in Italy.* J Epidemiol Community Health, 1994. **48**(5): p. 447-52.
225. Balder, H.F., et al., *Common and country-specific dietary patterns in four European cohort studies.* The Journal of nutrition, 2003. **133**(12): p. 4246-51.
226. Rahman, P., et al., *The Newfoundland population: a unique resource for genetic investigation of complex diseases.* Human molecular genetics, 2003. **12 Spec No 2**: p. R167-72.
227. *Statistics Canada. Farm population and total population by rural and urban population, by province.* 2008 [cited 2011 May 27]; Available from: http://www40.statcan.gc.ca/l01/cst01/agrc42b-eng.htm.
228. Hanrahan, M., *A veritable scoff: sources on foodways and nutrition in Newfoundland and Labrador*2001, St. John's, NL: Flanker Press.
229. Yang, Q., et al., *Family history score as a predictor of breast cancer mortality: prospective data from*

the Cancer Prevention Study II, United States, 1982-1991. American journal of epidemiology, 1998. **147**(7): p. 652-9.

230. Sun, Z., et al., *Reported Intake of Selected Micronutrients and Risk of Colorectal Cancer: Results from a Large Population-based Case-control Study in Newfoundland, Labrador and Ontario, Canada.* Anticancer research, 2012. **32**(2): p. 687-96.
231. DiStefano, C., M. Zhu, and D. Mîndrilă, *Understanding and Using Factor Scores: Considerations for the Applied Researcher.* Practical Assessment, Research & Evaluation, 2009. **14**(20).
232. Bentler, P.M., *Comparative fit indexes in structural models.* Psychological bulletin, 1990. **107**(2): p. 238-46.
233. Hu, L.T. and P.M. Bentler, *Cutoff Criteria for Fit Indexes in Covariance Structure Analysis: Conventional Criteria Versus New Alternatives.* Structural Equation Modeling-a Multidisciplinary Journal, 1999. **6**(1): p. 1-55.
234. Hair, J.F., *Multivariate data analysis with readings.* 4th ed1995, Englewood Cliffs, N.J.: Prentice Hall. xvii, 745, 12 p.
235. Schulze, M.B., et al., *Dietary patterns and their association with food and nutrient intake in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study.* The British journal of nutrition, 2001. **85**(3): p. 363-73.
236. Hu, F.B., et al., *Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire.* The American journal of clinical nutrition, 1999. **69**(2): p. 243-9.
237. Slattery, M.L., et al., *Eating patterns and risk of colon cancer.* Am J Epidemiol, 1998. **148**(1): p. 4-16.
238. Jackson, J.L., et al. *Introduction to Structural Equation Modeling.* [cited 2011 12/05]; Available from: http://www.sgim.org/userfiles/file/AMHandouts/AM05/handouts/pa08.pdf.
239. Mikolajczak, M., et al., *Psychometric properties of the Trait Emotional Intelligence Questionnaire: factor structure, reliability, construct, and incremental validity in a French-speaking population.* Journal of personality assessment, 2007. **88**(3): p. 338-53.

Appendices

Appendix 1. Personal History Questionnaire

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

What date are you filling out this questionnaire? _____/_____/_____

Day Month Year

Identifying information

1. Are you male or female?
   O male
   O female

2. What is your date of birth?
   ___ ___ years
   O don't know

2. What is your age?
   day ___ ___
   month ___ ___
   year ___ ___
   O don't know day
   O don't know month
   O don't know year

3. Are you a twin or triplet?
   O yes, a twin
   O yes, other multiple (triplet, quadruplet, etc.): _____
   Please specify
   O no
   O 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?
   O yes
   O no
   O don't know

5. What is your marital status?
   O currently married or living as married
   O separated
   O divorced
   O widowed
   O single or never married
   O don't know

6. Have you ever had a test for blood in your stool, called a smear test or a hemoccult? This test is frequently done as part of a routine physical examination, or it can be done at home.

O yes
O no → Please go to # 7
O don't know → Please go to # 7

6a. When did you first have this test?

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

6b. What were the reasons for your first test? Please tick all that apply.

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

6c. How many times have you had a hemoccult test?

___ number of hemoccult tests
O don't know

6d. If you have had a hemoccult test more than once, when did you last have this test?

age when last tested ___ ___
or
year of last test ___ ___ ___ ___
O 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.

O yes
O no → Please go to # 9
O don't know → Please go to # 9

8a. When did you first have this test?

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

8b. What were the reasons for your first

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.

O yes
O no → Please go to # 8
O don't know → Please go to # 8

7a. When did you first have this test?

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

7b. What were the reasons for your first sigmoidoscopy? Please tick all that apply.

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

7c. How many times have you had a sigmoidoscopy?

___ number of sigmoidoscopies
O 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 ___ ___ ___ ___
O 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 several inches.

O yes
O no → Please go to # 10
O don't know → Please go to # 10

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

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

colonoscopy? Please tick all that apply.

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

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

___ number of colonoscopies
O 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 ___ ___ ___ ___
O don't know

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

O yes
O no
O don't know

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

age at last diagnosis ___ ___
or
year of last diagnosis ___ ___ ___ ___
O don't know

9d. Do you know what kind of polyps they were?

O benign
O adenomatous (pre-cancerous)
O hyperplastic
O other: _____
Please specify
O 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.)

O yes
O no → Please go to # 10
O don't know → Please go to # 10

9f. When did you first have polyps removed?

age at first polypectomy ___ ___
or
year of first polypectomy ___ ___ ___ ___
O don't know

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

O yes
O no
O don't know

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

age at first polypectomy ___ ___
or
year of first polypectomy ___ ___ ___ ___
O 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.

O yes
O no → Please go to # 12
O don't know → Please go to # 12

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

age when first tested ___ ___
or
year of first test ___ ___ ___ ___
O 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) & rectum. It is not a stomach ulcer.

O yes
O no → Please go to # 13
O don't know → Please go to # 13

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

10. Has a doctor ever told you that you had familial adenmotaous 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.

O yes
O no → Please go to # 11
O don't know → Please go to # 11

10a. When did your doctor first tell you that you had FAP?
age at first diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O don't know

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

age at first diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O 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. and small intestine.

O yes
O no → Please go to # 15
O don't know → Please go to # 15

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

age at first diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O don't know

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

O yes
O no → Please go to # 16
O don't know → Please go to # 16

Was it completed removed, or was only part of it removed?
O completed removed
O partly removed

age at first diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O 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 diarrhea and constipation. It is sometimes called IBS, or spastic colon.

O yes
O no → Please go to # 14
O don't know → Please go to # 14

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

O yes
O no → Please go to # 16
O don't know → Please go to # 16

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

age at last operation ___ ___
or
year of last operation ___ ___ ___ ___
O don't know

16. Have you had your gallbladder removed?

O yes
O no → Please go to # 17
O don't know → Please go to # 17

16a. When did you have your gallbladder removed?

age at operation ___ ___
or
year of operation ___ ___ ___ ___
O 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.

O yes
O no → Please go to # 14
O don't know → Please go to # 14

O 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 ___ ___ ___ ___
O don't know

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

age at first diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O don't know

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

O yes
O no → Please go to # 18
O don't know → Please go to # 18

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

O pills
O insulin injections
O both
O 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	O	O

17e. About one year before your recent cancer diagnosis, were you taking it?

	Pills	Insulin
O yes	O	O
O no	O	O
O don't know	O	O

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

	Pills	Insulin
number of moths or	___ ___	___ ___
number of years	___ ___	___ ___
don't know	O	O

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

O yes
O no → Please go to # 19
O don't know → Please go to # 19

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

age at diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O don't know

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

O yes
O no → Please go to # 19
O 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 or
O don't know

18d. About one year before your recent cancer diagnosis, were you taking it?

O yes
O no
O don't know

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

___ ___ number of months or
___ ___ number of years
O 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.

O yes
O no → Please go to # 20
O don't know → Please go to # 20

19a. What 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?

O yes
O no → Please go to # 20
O 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 or
O don't know

19d. About one year before your recent cancer diagnosis, were you taking it?

O yes
O no
O don't know

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

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

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

O yes
O no → Please go to # 24
O don't know → Please go to # 24

20a. What type of cancer was it?
_____ cancer

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

age at diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O don't know

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

O yes
O no
O don't know

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

O yes
O no → Please go to # 24
O don't know → Please go to # 24

21a. What type of cancer was it?
_____ cancer

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

age at diagnosis ___ ___
or
year of diagnosis ___ ___ ___ ___
O don't know

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

O yes
O no
O don't know

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

O yes

Medications

Have you ever taken any of the following medications regular (at least twice a week

O no → Please go to # 24
O 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?

O yes
O no
O don't know

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

O yes
O no → Please go to # 24
O don't know → Please go to # 24

22a. 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?

O yes
O no
O don't know

for more than a month)?

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

O yes
O no → Please go to # 25
O 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
O don't know

24b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O 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
O 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 Tylenod, Anacin-3, Panadol)

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

O yes
O no → Please go to # 26
O 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
O don't know

25b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O 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
O don't know

O yes
O no → Please go to # 27
O 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
O don't know

26b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O 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
O 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, FibreCon. Serutan, psyllium)

O yes
O no → Please go to # 28
O 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.

28. Other laxatives (such as Ex-Lax, Correctol, Dulcolax, Senokot, Colace, castor, cod liver oil, mineral oil, milk of magnesia, lactulose, Epsom salts)

O yes
O no → Please go to # 29
O 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
O don't know

27b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O 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
O don't know

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

28b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O 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
O 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)

O yes
O no → Please go to # 28
O don't know → Please go to # 28

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
O don't know

29b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes

30. Folic acid or folate pills or tablets

O yes
O no → Please go to # 31
O 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
O don't know

30b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes

O no
O 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
O don't know

O no
O 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
O 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

O yes
O no → Please go to # 32
O don't know → Please go to # 32

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

O yes
O no → If female, Please go to # 33 If male. Please go to # 44
O don't know → If female, Please go to # 33 If male. Please go to # 44

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
O don't know

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
O don't know

29b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O don't know

32b. About one year before your recent cancer diagnosis, were you taking it regularly?

O yes
O no
O 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
O 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
O 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
O don't know
O never had a menstrual period

34. Have you ever been pregnant?

O yes
O no → Please go to # 35
O 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
O 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. _

O never
___ ___ number of pregnancies with more than one baby
O 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.

O never
___ ___ number of pregnancies lasting 6 months or longer
O don't know

34c. How many of your pregnancies resulted in live births?

O never
___ ___ number of pregnancies with live-born children
O don't know

34d. How old were you at the first live birth?

age at first birth ___ ___ or
year of first birth ___ ___ ___ ___
O don't know

34e. How old were you at the last live birth?

age at last birth ___ ___ or
year of last birth ___ ___ ___ ___
O don't know

35. Have you ever used birth control pills or other hormonal contraceptives (implants or injections) for at least one year?

O yes
O no → Please go to # 36
O 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 ___ ___ ___ ___
O don't know

35a. Were you still using hormonal contraceptives about one year before your recent cancer diagnosis?

O yes
O no
O 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
O 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 hormonal replacement therapy (HRT) or progesterones, progesttins or withdrawal bleeding.

O yes → Please go to #42
O no
O don't know → Please go to #42

Have your periods stopped permanently or only temporarily due to pregnancy, breast-feeding, or other conditions?

O permanently
O temporarily → Please go to #42

37. How old were you when your periods stopped permanently?

age they stopped ___ ___ or
year they stopped ___ ___ ___ ___
O don't know

38. Why did your menstrual periods stop permanently? Please tick all that apply.

O natural menopause
O surgery
O radiation or chemotherapy
O other reason
Please specify: _____
O Don't know

Please complete the next few questions which ask about surgeries you may have had.

39. Hysterectomy (only the uterus or womb Removed)

O yes
O no
O don't know
>age when removed ___ ___ or
years when removed ___ ___ ___ ___
O don't know

39a. Hysterectomy with one ovary or part of an Ovary removed)

O yes
O no
O don't know
>age when removed ___ ___ or
years when removed ___ ___ ___ ___
O don't know

39b. Hysterectomy with both ovaries removed

O yes
O no
O don't know
>age when removed ___ ___ or
years when removed ___ ___ ___ ___
O don't know

39c. One ovary removed, completely or partly, without hysterectomy

O yes
O no
O don't know
>age when removed ___ ___ or
years when removed ___ ___ ___ ___
O don't know

39d. Both ovaries removed without hysterectomy

O yes
O no
O don't know
>age when removed ___ ___ or
years when removed ___ ___ ___ ___
O don't know

40. If you had radiation or chemotherapy, when did you first have it?

42a. Were you still having menstrual periods when you first took these hormones?

O yes
O no
O don't know

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

O had radiation or chemotherapy
>age when this was given ___ ___ or
year when this was given ___ ___ ___ _
O don't know
O never had radiation or chemotherapy

41. if your periods stopped permanently for any reason other than surgery, radiation or chemotherapy, when did you this occur?

O other reason
Please specify: _____
>age when occurred ___ ___ or
year when occurred ___ ___ ___ ___
O don't know
O not applicable

42. Doctors prescribe hormonal 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 hormonal replacement therapy prescribed by a doctor and in the form of a pill or a patch?

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

O yes
O no → Please go to #43
O don't know → Please go to #43

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?

O yes
O no → Please go to #43
O 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 ___ ___ ___ ___
O don't know

hormone replacement therapy?

O yes
O no
O don't know
>How old were you when you first took estrogen-only medication?

age when first taken ___ ___ or
years when first taken ___ ___ ___ _
O don't know

42c. Were you still using estrogen-only medication for hormone replacement therapy about one year before your recent cancer diagnosis?

O yes
O no
O 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
O don't know

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

O yes
O no → Please go to #44
O possibly – I have participated in a clinical trial for tamoxifen or other anti-estrogen medication
O don't know
>What anti-estrogen medication did you take? Please tick all that apply.

O tamoxifen
O raloxifene
O other: _____
Please specify

42f. Were you still using progesterone or progestin medication about one year before your recent cancer diagnosis?

O yes
O no
O 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
O don't know

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 ___ ___ ___ ___
O don't know

43b. Were you still using tamoxifen, raloxifene or other anti- estrogen medication about one year before your recent cancer diagnosis?

O yes
O no
O 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
O don't know

Diet

44. About one year before your recent cancer diagnosis, on average, how often did you eat a piece serving of fruit?
(A serving of fruit is: 1 medium-sized fresh fruit; ½ cup of chopped, cooked or canned fruit; ¼ 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
O don't know

45. About one year before your recent cancer diagnosis, on average, how often did you eat a piece serving of vegetables?
(A serving of vegetables is: 1 medium-sized fresh vegetables; ½ cup of chopped, cooked or chopped vegetables; 6 ounces of vegetable juice (50%-100% pure juice).) Please choose one of the following.

___ ___ servings per day or
___ ___ servings per week or
___ ___ servings per month
O don't know

46. About one year before your recent cancer diagnosis, 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.)

___ ___ servings per day or
___ ___ servings per week or
___ ___ servings per month
O don't eat red meat → Please go to #47
O don't know

46a. About one year before your recent cancer diagnosis, on average, how often did you eat a serving of red meat that was cooked by broiling, grilling, barbecueing 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
O don't eat red meat that was cooked by these methods → Please go to #47
O 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?

O lightly browned
O medium browned
O heavily browned or blackened
O don't know

What was its inside appearance? (how well done it was)?

O red (rare)
O pink (medium)
O brown (well-done)
O don't know

47. About one year before your recent cancer diagnosis, 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
O don't eat red meat that was cooked by these methods → Please go to #48
O don't know

47a. About one year before your recent cancer diagnosis, on average, how often did you eat a serving of chicken that was cooked by broiling, grilling, barbecueing 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
O don't eat chicken that was cooked by these methods → Please go to #48
O don't know

47b. On average, when you ate chicken cooked by these methods, which of the following best describes its appearance?

What was its outside appearance?

O lightly browned

O medium browned
O heavily browned or blackened
O don't know

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

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

Activity Please specify		For how many years?	During those years, for many months per year?	During those months, on average, for how many minutes or hours per week?
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
		___ ___ years	___ ___ months	__ minutes per week / __hours per week

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

_____ occupation

O don't know

If you are younger than 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 many months per year?	During those months, on average, for how many minutes or hours per week?
Walking	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Jogging (running slower than a mile in 10 minutes)	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Running (running faster than a mile in 10 minutes)	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Bicycling (including using an exercise bicycle	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Swimming laps	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Tennis, squash racquetball	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Calisthenics, aerobics, vigorous dance (including ballet), using a rowing machine, lifting weights	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Football, soccer rugby, basketball	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Heavy household work (examples: using a non-power mower, shoveling, moving heavy loads, scrubbing floors)	O yes → O no	___ ___ years	___ ___ months	__ minutes per week / __hours per week

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

Activity Please specify	For how many years?	During those years, for many months per year?	During those months, on average, for how many minutes or

				hours per week?
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
		___ ___ years	___ ___ months	__ minutes per week / __hours per week

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

_____ occupation

O don't know

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

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

52. In your 50s, 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 many months per year?	During those months, on average, for how many minutes or hours per week?
Walking	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Jogging (running slower than a mile in	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week

10 minutes)

Running (running faster than a mile in 10 minutes)	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Bicycling (including using an exercise bicycle	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Swimming laps	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Tennis, squash racquetball	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Calisthenics, aerobics, vigorous dance (including ballet), using a rowing machine, lifting weights	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Football, soccer rugby, basketball	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week
Heavy household work (examples: using a non-power mower, shoveling, moving heavy loads, scrubbing floors)	O yes → O no →	___ ___ years	___ ___ months	__ minutes per week / __hours per week

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

Activity Please specify		For how many years?	During those years, for many months per year?	During those months, on average, for how many minutes or hours per week?
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week

_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
_____	→	___ ___ years	___ ___ months	__ minutes per week / __hours per week
		___ ___ years	___ ___ months	__ minutes per week / __hours per week

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

_____ occupation

O don't know

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?
Beer, hard cider (at least 3% alcohol)	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 12 ounce cans or bottles O per day O per week O don't know
Wine	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 4 ounce glasses of wine O per day O per week O don't know
Sake, sherry, port	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 1 ounce servings O per day O per week O don't know
Spirits, liquor	O yes →	___ ___ years consumed	___ ___ number of 1 ounce

mixed drinks, brandy, liqueurs	O no O don't know		___ ___ number of 1 ounce shots liquor or spirits O per day O per week O 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
O 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.

___ ___ years consumed
O 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 cider (at least 3% alcohol)	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 12 ounce cans or bottles O per day O per week O don't know
Wine	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 4 ounce glasses of wine O per day O per week O don't know
Sake, sherry, port	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 1 ounce servings O per day O per week O don't know
Spirits, liquor mixed drinks, brandy, liqueurs	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 1 ounce shots liquor or spirits O per day O per week O 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
O 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.

___ ___ years consumed
O 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 50s.

60. In your 50s, 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)	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 12 ounce cans or bottles O per day O per week O don't know
Wine	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 4 ounce glasses of wine O per day O per week O don't know
Sake, sherry, port	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 1 ounce servings O per day O per week O don't know
Spirits, liquor mixed drinks, brandy, liqueurs	O yes → O no O don't know	___ ___ years consumed	___ ___ number of 1 ounce shots liquor or spirits O per day O per week O don't know

61. 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
O 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.

___ ___ years consumed
O never consumed alcohol

Smoking

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

O yes
O no → Please go to #64
O 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 ___ ___ ___ ___
O don't know

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

___ ___ ___ ___ cigarettes per day
O don't know

63c. About one year before your recent cancer diagnosis, were you still smoking at least one cigarette a day?

O yes
O no
O don't know

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

O yes
O no → Please go to #63f
O don't know → Please go to #63f

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

age at first use ___ ___ or
year of first use ___ ___ ___ ___
O 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.)

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

O yes
O no → Please go to #65
O 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 ___ ___ ___ ___
O don't know

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

___ ___ ___ ___ cigarettes per month
O don't know

64c. About one year before your recent cancer diagnosis, were you still smoking at least one cigar a month?

O yes
O no
O don't know

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

O yes
O no → Please go to #64f
O don't know → Please go to #64f

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

age at first use ___ ___ or
year of first use ___ ___ ___ ___
O 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
O don't know

___ ___ ___ ___ total number of years
O don't know

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

O yes
O no → Please go to #66
O 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 ___ ___ ___ ___
O don't know

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

___ ___ ___ ___ pipe per month
O don't know

65c. About one year before your recent cancer diagnosis, were you still smoking at least one pipe a month?

O yes
O no
O don't know

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

O yes
O no → Please go to #65f
O don't know → Please go to #65f

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

age at first use ___ ___ or
year of first use ___ ___ ___ ___
O 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
O don't know

Height and Weight

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

___ feet ___ ___ inches
or
___ ___ ___ centimeters
O don't know

67. How much did you weigh about one year before your recent cancer diagnosis?

___ pounds
Or
___ ___ ___ kilograms
O don't know

Additional Information

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

O yes
O no
O don't know

Background Information

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

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

71. Country of birth sometimes affects disease risk. Please fill in country of birth for yourself, you 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	_____	O yes O no O don't know	O	O	O	O
Your mother	_____	O yes O no O don't know	O	O	O	O
Your father	_____	O yes O no O don't know	O	O	O	O
Your mother's mother	_____	O yes O no O don't know	O	O	O	O
Your mother's father	_____	O yes O no O don't know	O	O	O	O
Your father's mother	_____	O yes O no O don't know	O	O	O	O
Your father's father	_____	O yes O no O don't know	O	O	O	O

72. How many years have you lived in Canada?

O all my life
___ ___ number of years
O 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.

	You	Your mother	Your father	Your Mother's mother	Your Mother's father	Your Father's mother	Your Father's Father
Black, From Africa	O	O	O	O	O	O	O
Black, from Caribbean (Trinidad, Jamaica, Haiti)	O	O	O	O	O	O	O
Black from North America	O	O	O	O	O	O	O
Black, other	O	O	O	O	O	O	O
White	O	O	O	O	O	O	O
First Nations (Indian, Inuit)	O	O	O	O	O	O	O
North African (Egyptian)	O	O	O	O	O	O	O
Middle East (Iranian)	O	O	O	O	O	O	O
Filipino	O	O	O	O	O	O	O
Japanese	O	O	O	O	O	O	O
Korean	O	O	O	O	O	O	O
Chinese	O	O	O	O	O	O	O
Other South East Asian (Vietnamese)	O	O	O	O	O	O	O
South Asian (East Indian, Pakistani)	O	O	O	O	O	O	O
Other: Please specify	_____	_____	_____	_____	_____	_____	_____
Don't know	O	O	O	O	O	O	O

74. Which of the following categories best describes your total annual household income about one year before your recent diagnosis?

O no income
O less than $6,000
O $6,000 - $11,999
O $12,000 - $19,999
O $40,000 - $49,999
O $50,000 - $59,999
O $60,000 - $69,999
O $70,000 - $79,999

O $20,000 - $29,999
O $30,000 - $39,999
O $80,000 +
O 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: _____
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. Food Frequency Questionnaire

Canadian Study of Diet and Health

Memorial
University of Newfoundland

SAMUEL LUNENFELD RESEARCH INSTITUTE

Who this questionnaire is for and what it asks about:

This questionnaire is to be completed by the person taking part in this study:

Part I asks about the foods you ate about **one year before your diagnosis**.

Part II asks about vitamins and other dietary supplements that you may have used.

If possible, please return this questionnaire within two weeks.

The completed questionnaire should be sealed in the pre-paid envelope and mailed back to:

CRC-IHRT,
Room 1758E, Level 1, Health Science Centre,
300 Prince Phillip Drive,
St. John's, NL, Canada, A1B 9Z9.

If you have any questions about this form or the study, call our toll-free number, **1-888-908-4988.**

The information given to us in this questionnaire will be kept confidential.

Thank you for your time and assistance.

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HOW TO COMPLETE THIS QUESTIONNAIRE

We would like to know how often you ate certain foods **about one year before diagnosis,** and their amounts.

Section A ***(lists foods and portion sizes)***
Amounts are described in various ways, including the number of:

cups, teaspoons (tsp), ounces (oz), inches ("), pieces (e.g., 1 apple)
grams (gm), tablespoons (tbsp), millilitres (ml), centimetres (cm).

We want to know the ***Portion Size*** of your **USUAL SERVING.** We have given an example of an average portion size. If your portion size was different than the average, you can indicate this by putting an **X** or ✓in the circles for ***Smaller*** or ***Larger*** portion sizes. ***Smaller*** than average is about 25% or less than the average portion size, while ***Larger*** than average is about 25% or more than the average size. Leave the circle blank if your typical portion size was average.

Included with this questionnaire is a ***FOOD PHOTOGRAPH PAGE*** that shows small, medium and large portion sizes for vegetables, meat and chicken. Some questions ask you to refer to the photo page to help you choose your usual portion size.

Section B ***(asks about how often you ate certain foods one year before diagnosis)***
For each food item listed, choose **one** column (Per Day, Per Week, Per Month, or Never / Rarely) that best describes ***HOW OFTEN*** you ate or drank that item. For example, if you ate CREAM CHEESE 3 times a month during the year of interest, you would write (3) in the *PER MONTH* column. If you ate SWEET POTATOES only 2 times during the year of interest, you can place a checkmark (✓) in *the NEVER OR RARELY* column.

Section C ***(To be completed only for seasonal foods)***
Some foods (for example fresh fruit and vegetables) are not available throughout the year. **For foods that you do not eat all year round** (i.e. in season only), indicate the number of months of the year that you ate them.

Please complete each question as best you can. We know that it is difficult to recall exactly how often you ate something. If you are not certain, try to give your best estimate.

EXAMPLE	Section A				Section B YEAR BEFORE DIAGNOSIS				Section C
	FOOD	Average Portion Size	Your Portion Size, if NOT Average		HOW OFTEN? (Complete one column only)				If Ate Food in Season Only
			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
1	CREAM CHEESE	2 tbs/ 30 ml/ 1 oz	O	O			*3*		
2	CANTELOUPE	1/8 or 1 slice	O	O		*1*			*4*
3	SWEET POTATOES	1 medium/ ½ cup	O	O				√	

	Section A				Section B YEAR BEFORE DIAGNOSIS				Section C
	FOOD	Average Portion Size	Your Portion Size, if NOT Average		HOW OFTEN? (Complete one column only)				If Ate Food In Season Only
			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
	Dairy Products								
24	EGG (boiled, poached)	1 egg	O	O					
25	EGG (fried, scrambled, omelette)	1 egg	O	O					
26	CREAM CHEESE, Regular fat	2 tbs/ 30 ml/ 1 oz	O	O					
27	CHEESE, Regular fat (such as cheddar, Swiss, processed)	1 slice/ 30 g/ 1oz	O	O					
28	CHEESE, Light (6-15% fat, such as cream cheese, cheddar)	1 slice/ 30 g/ 1oz	O	O					
29	CHEESE, Ultra Light (5% fat or less, such as cheddar)	1 slice/ 30 g/ 1oz	O	O					
30	COTTAGE or RICOTTA CHEESE	125 ml/ ½ cup	O	O					
31	CREAM (coffee, whipping, sour or regular)	1 tbs/ 15 ml	O	O					
32	CREAM (half and half, light sour cream)	1 tbs/ 15 ml	O	O					
33	COFFEE WHITENER (non-dairy)	1 tbs/ 15 ml	O	O					
34	YOGURT, Regular (plain, 2.4% fat or more)	¾ cup/ 175 ml	O	O					
35	YOGURT, Light (plain, less than 2.4% fat)	¾ cup/ 175 ml	O	O					
36	YOGURT, Regular (fruit flavoured or frozen, 2.4% fat or more)	¾ cup/ 175 ml	O	O					
37	YOGURT, Light (fruit flavoured or frozen, less than 2.4% fat)	¾ cup/ 175 ml	O	O					
	Mixed Dishes								
38	SOUPS (creamed)	1 cup/ 250 ml	O	O					
39	SOUPS (non-creamed)	1 cup/ 250 ml	O	O					
40	PEA SOUP	1 cup/ 250 ml	O	O					
41	PASTA with meat sauce (spaghetti, lasagna)	1 cup/ 250 ml	O	O					
42	PASTA with tomato sauce (spaghetti)	1 cup/ 250 ml	O	O					
43	MIXED DISHES with cheese or cheese sauce (macaroni and cheese)	1 cup/ 250 ml	O	O					
44	PIZZA with meat	1 Medium slice	O	O					
45	PIZZA with vegetable only	1 Medium slice	O	O					

Section A					Section B YEAR BEFORE DIAGNOSIS				Section C
	FOOD	Average Portion Size	Your Portion Size, if NOT Average		HOW OFTEN? (Complete one column only)				If Ate Food In Season Only
			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
46	MEAT STEW with carrots, other vegetables	1 cup/ 250 ml/ photo A, medium	O	O					
47	CHILI with meat or Con Carne	1 cup/ 250 ml	O	O					
	Vegetables								
48	POTATOES (mashed, boiled, baked etc)	1 medium/ ½ cup/ 125 ml	O	O					
49	FRENCH FRIES or FRIED POTATOES	1 cup/ 250 ml	O	O					
50	CARROTS (raw or cooked)	1 medium/ ½ cup /125 ml	O	O					
51	BROCCOLI	1 cup/ 250 ml	O	O					
52	CABBAGE, COLESLAW	½ cup/ 125 ml	O	O					
53	CAULIFLOWER	½ cup/125 ml	O	O					
54	CORN	1 ear / ½ cup	O	O					
55	PEAS or LIMA BEANS	½ cup/125 ml	O	O					
56	GREEN or YELLOW BEANS	½ cup/125 ml	O	O					
57	BEANS or LENTILS (baked or boiled beans, kidney beans, chickpeas)	½ cup/125 ml cooked	O	O					
58	SPINACH and other green leafy vegetables (greens, collards, kale, mustard greens etc)	½ cup/125 ml cooked or 1 cup raw	O	O					
59	GREEN SALAD (with lettuce)	1 cup/ 250 ml	O	O					
60	CUCUMBER	½ cup/ 125 ml sliced	O	O					
61	TOMATOES (fresh)	1 medium/ ½ cup/ 125 ml	O	O					
62	TOMATOES (canned, pureed or sauce)	½ cup/125 ml	O	O					
63	ONIONS (raw or cooked)	½ cup/125 ml	O	O					
64	BEETS (boiled or pickled)	½ cup/125 ml	O	O					
65	TURNIPS or RUTABAGAS	1 medium/ ½ cup/125 ml	O	O					
66	OTHER ROOT VEGETABLES (sweet potatoes, yams, radish, etc)	½ cup/125 ml	O	O					
67	YELLOW SQUASH (winter type)	½ cup/125 ml	O	O					

Section A					Section B YEAR BEFORE DIAGNOSIS				Section C
	FOOD	Average Portion Size	Your Portion Size, if NOT Average		HOW OFTEN? (Complete one column only)				If Ate Food In Season Only
			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
90	LIVER	85 g/ 3 oz	O	O					
91	FRIED CHICKEN	photo C, medium	O	O					
92	CHICKEN / TURKEY (roasted or stewed)	photo C, medium	O	O					
93	CHICKEN / TURKEY, SKIN REMOVED	photo C, medium	O	O					
94	SALTED/ DRIED MEAT	photo C, small	O	O					
95	PICKLED MEAT (brined)	photo C, small	O	O					
96	SHELLFISH (shrimp, lobster, crab)	85 g/ 3 oz/ photo C, small	O	O					
97	FRIED FISH	175 g/ 6 oz/ photo B, medium	O	O					
98	FISH (baked or broiled)	175 g/ 6 oz/ photo B, medium	O	O					
99	CANNED FISH (tuna, salmon)	½ can/ 48 ml/ 1.7 oz	O	O					
100	SMOKED FISH or LOX	85 g/ 3 oz/ photo C, small	O	O					
101	SALTED/ DRIED FISH	85 g/ 3 oz/ photo C, small	O	O					
102	PICKLED FISH	85 g/ 3 oz/ photo C, small	O	O					
103	SEA-BIRDS, SEAL	85 g/ 3 oz/ photo C, small	O	O					
104	CARIBOU, MOOSE	85 g/ 3 oz/ photo C, small	O	O					
105	PARTRIDGE, OTHER WILD BIRDS	85 g/ 3 oz/ photo C, small	O	O					
	Cereals and Grains								
106	BRAN or GRANOLA CEREALS (including All Bran)	½ cup/ 125 ml	O	O					
107	WHOLE WHEAT CEREALS (such as shredded wheat)	½ cup/ 125 ml/ 1 biscuit	O	O					
108	CEREALS, NOT SUGAR COATED (such as Special K)	½ cup/ 125 ml	O	O					
109	HOT CEREALS (for example: oatmeal)	½ cup/ 125 ml	O	O					
110	SUGAR COATED CEREALS	½ cup/ 125 ml	O	O					
111	OTHER BREAKFAST CEREALS	½ cup/ 125 ml	O	O					
112	SUGAR ON CEREAL	1 tsp	O	O					

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			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
90	LIVER	85 g/ 3 oz	O	O					
91	FRIED CHICKEN	photo C, medium	O	O					
92	CHICKEN / TURKEY (roasted or stewed)	photo C, medium	O	O					
93	CHICKEN / TURKEY, SKIN REMOVED	photo C, medium	O	O					
94	SALTED/ DRIED MEAT	photo C, small	O	O					
95	PICKLED MEAT (brined)	photo C, small	O	O					
96	SHELLFISH (shrimp, lobster, crab)	85 g/ 3 oz/ photo C, small	O	O					
97	FRIED FISH	175 g/ 6 oz/ photo B, medium	O	O					
98	FISH (baked or broiled)	175 g/ 6 oz/ photo B, medium	O	O					
99	CANNED FISH (tuna, salmon)	½ can/ 48 ml/ 1.7 oz	O	O					
100	SMOKED FISH or LOX	85 g/ 3 oz/ photo C, small	O	O					
101	SALTED/ DRIED FISH	85 g/ 3 oz/ photo C, small	O	O					
102	PICKLED FISH	85 g/ 3 oz/ photo C, small	O	O					
103	SEA-BIRDS, SEAL	85 g/ 3 oz/ photo C, small	O	O					
104	CARIBOU, MOOSE	85 g/ 3 oz/ photo C, small	O	O					
105	PARTRIDGE, OTHER WILD BIRDS	85 g/ 3 oz/ photo C, small	O	O					
	Cereals and Grains								
106	BRAN or GRANOLA CEREALS (including All Bran)	½ cup/ 125 ml	O	O					
107	WHOLE WHEAT CEREALS (such as shredded wheat)	½ cup/ 125 ml/ 1 biscuit	O	O					
108	CEREALS, NOT SUGAR COATED (such as Special K)	½ cup/ 125 ml	O	O					
109	HOT CEREALS (for example oatmeal)	½ cup/ 125 ml	O	O					
110	SUGAR COATED CEREALS	½ cup/ 125 ml	O	O					
111	OTHER BREAKFAST CEREALS	½ cup/ 125 ml	O	O					
112	SUGAR ON CEREAL	1 tsp	O	O					

Section A					Section B YEAR BEFORE DIAGNOSIS				Section C
	FOOD	Average Portion Size	Your Portion Size, if NOT Average		HOW OFTEN? (Complete one column only)				If Ate Food In Season Only
			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
113	100% WHOLE GRAIN or DARK BREAD	1 slice	O	O					
114	60% WHOLE GRAIN, LIGHT RYE	1 slice	O	O					
115	WHITE BREAD	1 slice	O	O					
116	WHITE BREAD ROLLS (including hot dog buns etc)	1 roll	O	O					
117	WHOLE WHEAT ROLLS	1 roll	O	O					
118	CRACKERS (snack or soda type)	2	O	O					
119	BRAN/OAT MUFFIN	1 medium, ½ extra large	O	O					
120	OTHER MUFFIN (plain cake, with berries)	1 medium, ½ extra large	O	O					
121	PANCAKES, WAFFLES	1	O	O					
122	MACARONI, SPAGHETTI, NOODLES (plain)	1 cup cooked/ 250 ml	O	O					
123	RICE	½ cup cooked/ 125 ml	O	O					
124	CRISP SNACKS (potato chips, popcorn, pretzels etc)	small bag or 1 cup	O	O					
	Fruits								
125	APPLE, PEAR	1	O	O					
126	CITRUS FRUITS (orange, grapefruit)	1 orange, ½ grapefruit	O	O					
127	BERRIES (strawberries, blueberries, bakeapples)	½ cup/ 125 ml	O	O					
128	GRAPES	½ cup/ 125 ml	O	O					
129	BANANA	1	O	O					
130	PEACH, PLUM, NECTARINE, APRICOT	1	O	O					
131	CANTALOUPE	1/8 or 1 slice	O	O					
132	WATERMELON	1 wedge, 3" base	O	O					
133	HONEYDEW MELON	1/8 or 1 slice	O	O					
134	MANGO	1	O	O					
135	PAPAYA	1	O	O					
136	APPLESAUCE	½ cup/ 125 ml	O	O					

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			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
137	DRIED FRUITS (raisins, dates, prunes)	2 tbsp/ 2 dates	O	O					
138	CANNED FRUIT (all kinds)	½ cup/ 125 ml	O	O					
139	ALL OTHER FRUIT (fresh kiwi, pomegranate, etc.)	1	O	O					
	Desserts and Sweets								
140	CAKES	1 slice, 2" x 4" x 1"	O	O					
141	PIES and TARTS	1 slice	O	O					
142	DONUTS and SWEET ROLLS	1	O	O					
143	COOKIES	1	O	O					
144	ICE CREAM	½ cup/ 125 ml	O	O					
145	LIGHT or DIET ICE CREAM	½ cup/ 125 ml	O	O					
146	PUDDING	½ cup/ 125 ml	O	O					
147	DIET or LIGHT PUDDING	½ cup/ 125 ml	O	O					
148	JELLO	½ cup/ 125 ml	O	O					
149	POPSICLES, FREEZIES	1	O	O					
150	CHOCOLATE BAR and CHOCOLATE CANDY	1 bar / 50g or 5 candy size	O	O					
151	CANDY (without chocolate)	1 caramel	O	O					
	Miscellaneous								
152	TOFU, TEMPEH	½ cup, 2" x 2" x 1" piece	O	O					
153	KETCHUP	1 tbs	O	O					
154	MAYONNAISE/ MIRACLE WHIP, Regular fat (on bread, salad, meat, etc)	1 tbs	O	O					
155	MAYONNAISE/ MIRACLE WHIP, Light (on bread, salad, meat, etc)	1 tbs	O	O					
156	SALAD DRESSING, Regular fat (French, Italian etc)	1 tbs	O	O					
157	OIL (in cooking)	1 tsp	O	O					

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			Smaller	Larger	per DAY (enter a number)	per WEEK (enter a number)	per MONTH (enter a number)	NEVER or RARELY (check)	enter Months per Year
158	BUTTER (on vegetables or bread, exclude use in baked and mixed dishes)	1 pat/ 1 tsp	O	O					
159	MARGARINE (on vegetables or bread, exclude use in baked or mixed dishes)	1 pat/ 1 tsp	O	O					
160	PEANUT BUTTER	1 tbs	O	O					
161	PEANUTS	30g/ 1 oz	O	O					
162	OTHER NUTS	30g /1 oz	O	O					
163	JAM, JELLY, HONEY, SYRUP	1 tbs	O	O					
164	GRAVY	4 tbs	O	O					
165	CHOCOLATE or STRAWBERRY SYRUP	1 tbs	O	O					
166	CHOCOLATE SPREADS	1 tbs	O	O					
167	SAUCES (white, cream, Mornay)	30 ml/ 1oz/ 2 tbs	O	O					
168	WHEAT BRAN	1 tbs	O	O					
169	WHEAT GERM	1 tbs	O	O					

Continue on next page ⟶

Now we would like to ask you a few questions about how you prepared certain foods ABOUT ONE YEAR BEFORE DIAGNOSIS and whether you followed any special diets. For the following questions, please check the circle or fill in the appropriate answer:

1. About 1 year before diagnosis, how much of the visible fat on your meat did you eat?

- O Most of it.
- O Some of it.
- O As little as possible.
- O Do not eat meat

2. About 1 year before diagnosis, how often did you eat the skin on chicken?

- O Most of it.
- O Some of it.
- O As little as possible.
- O Do not eat chicken

3. About 1 year before diagnosis, what kind of fat did you usually use for stir/pan frying?

- O Vegetable oil
- O Vegetable shortening
- O Lard/ pork fat
- O Butter
- O Margarine
- O Do not add fat or oil
- O Other, please specify _____

4. About 1 year before diagnosis, what kind of fat did you usually use for deep frying?

- O Vegetable oil
- O Vegetable shortening
- O Lard/ pork fat
- O Butter
- O Margarine
- O Do not fry
- O Other, please specify _____

5. About 1 year before diagnosis, what kind of fat did you usually use for baking?

- O Butter
- O Margarine
- O Vegetable Oil
- O Vegetable shortening
- O Lard/ pork fat
- O Do not bake

6. About 1 year before diagnosis, what type of oil did you use in other preparations (for example, in salad dressings)?

_____

7. About 1 year before diagnosis, what type of the following items did you usually use? *Please check one box per line.*

Mayonnaise/Miracle Whip
O regular O light O both O none

Cream cheese
O regular O light O both O none

8. About 1 year before diagnosis, were you a (*please check one box only*):

- O Non-vegetarian (eats all meat, chicken, fowl)
- O Partly non-vegetarian (eats chicken, fish, no meat)
- O Vegan (eats no dairy, no eggs, no meat)
- O Lacto-vegetarian (eats dairy, no eggs, no meat)
- O Lacto-ovo vegetarian (eats dairy & eggs, no meat)

9. About 1 year before diagnosis, were you on a special diet?

O No O Yes

If yes, what type of diet?

- O To lose Weight
- O To lower cholesterol
- O Diabetes
- O Heart disease
- O Hypertension
- O Gastric ulcer
- O Bowel disease
- O Low fat
- O High fibre
- O Other type: _____

If yes, how long were you on the special diet?

_____

PART 2 - USE OF VITAMINS AND DIETARY SUPPLEMENTS

Now we would like to know about your use of vitamins and dietary supplements.
ABOUT ONE YEAR BEFORE DIAGNOSIS, did you take any of the following? If *Yes*, then specify usual brand and amount and how long you took them.

Vitamin and Amount – if used, ⇒	How many pills did you take per week?	How long had you taken them?
Vitamin C (EXAMPLE) O None O Below 500 Ø 500-1000 O above 1000 mg	0 5 per week	2 4 months
Multivitamins that include minerals O No O Yes If yes, usual brand _____ ⇒	per week	months
Multivitamins, no minerals O No O Yes If yes, usual brand _____	per week	months
B Complex vitamins O No O Yes If yes, usual brand _____	per week	months
In the following items, DO NOT INCLUDE use of the above MULTIVITAMINS		
Vitamin A O None O Below 10000 O 10000-15000 O above 15000 IU	per week	months
Vitamin C O None O Below 500 O 500-1000 O above 1000 mg	per week	months
Vitamin E O None O Below 400 O 400-800 O above 800 IU	per week	months
Beta-carotene O None O Below 10000 O 10000-15000 O above 15000 IU	per week	months
Folic acid O None O Below 1.0 O 1.0 mg O above 1.0 mg*	per week	months
Calcium O None O Below 250 O 250-500 O above 500 mg	per week	months
Iron O None O Below 100 O 100-200 O above 200 mg	per week	months
Other dietary supplements (e.g., yeast, cod liver oil, etc) O No O Yes, specify type: _____	per week	months
_____	per week	months

* 1 mg = 1000 micrograms

We welcome any other information or comments that you would like to give us:

_____

_____

_____

THANK YOU VERY MUCH for your assistance in this research!

For Office Use Only

Study #: _____

Interviewer: _____

Date completed (D/M/Y): _____