THE IMPACT OF ALCOHOL INTAKE AND TOBACCO SMOKING ON COLORECTAL CANCER AND METHODOLOGICAL ISSUES OF RISK MEASURES

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The Impact of Alcohol Intake and Tobacco Smoking on Colorectal Cancer and Methodological Issues of Risk Measures

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Abstract

Between 1999 and 2003, a large colorectal cancer (CRC) case-control study was conducted in Newfoundland and Labrador (NL). The primary aim of this thesis was to explore relations between use of alcohol and tobacco and CRC risk. The specific objectives were to (i) determine the extent of non-participation bias by comparing the differences in demographics between participants and non-participants; (ii) explore mis-reporting for tobacco and alcohol use using provincial sales data and the Canadian Community Health Survey (CCHS) 1.1 and 3.1 data for alcohol and tobacco; (iii) examine impact of tobacco smoking on risk of CRC; (iv) examine impact of alcohol consumption on risk of CRC

Newly diagnosed CRC cases identified in 1999-2003 in NL, Canada were frequency-matched by age and sex with controls selected using random digit dialing (RDD). Cases (n = 702) and controls (n = 717) completed self-administered questionnaires assessing health and lifestyle variables. Measures of tobacco use included type of tobacco, age of initiation of smoking, years of smoking, years since started smoking, number of cigarettes smoked daily, pack years, and years since abstention from smoking. Estimates of alcohol intake included types of beverage, years of drinking, and number of drinks daily. Odds ratios were estimated using multivariate logistic regression.

The study found a 49% higher risk of CRC among cigarette smokers than non-smokers. The risk tended to increase significantly with cigarette smoking years, amount of cigarettes smoked daily, cigarette pack years and the risk significantly decreased with years of abstention from smoking. Smoking demonstrated a stronger cancer risk in men

than women, in drinkers than non-drinkers and in obese men than obese women. The study demonstrated that the effect of alcohol intake on odds of developing CRC differed by weight status. Alcohol consumption tended to reduce the odds of developing CRC in non-obese. In the obese (BMI $\geq$ 30), the odds of CRC (OR = 2.25) were greater in drinkers than in non-drinkers. The odds of developing CRC increased with number of drinking years and numbers of drinks daily in obese. The effect of drinking on CRC risk was stronger among obese subjects who smoked.

In conclusion, this thesis reported that cigarette smoking increased the risk of CRC. Alcohol drinking decreased CRC risk in non-obese and cigarette non-smokers, but drinking increased the risk of CRC in the presence of cigarette smoking and obesity. Low participation rates may limit the generalizability of the results.

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The study was based on the database owned by the Canadian Institutes of Health Research Team in Interdisciplinary Research on Colorectal Cancer (CIHR TIRCRC, formerly known as crCIHRt) consisting of health researchers in the provinces of Ontario and Newfoundland and Labrador who are conducting serially linked colorectal cancer studies that involve a wide range of scientific disciplines. Therefore, I would like to thank Professor Wang and his colleagues for permitting access to the database. Thanks to Statistics Canada and Health Canada for their contributions of the sales data of alcoholic beverages and tobacco, the population data and the data of the Canadian Community Health Survey 1.1 and 3.1.

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Glossary

APC: Adenomatous polyposis coli

BMI: Body mass index

CAI: Computer-assisted interviewing

CAPI: Computer-assisted personal interviewing

CAS: Canadian Addictions Survey

CCHS: Canadian Community Health Survey

CI: Confidence interval

CIHR: Canadian Institutes of Health Research

CRC: Colorectal cancer

CTUMS: Canadian Tobacco Use Monitoring Survey

FAP: Familial adenomatous polyposis

FFQ: Food frequency questionnaire

FHQ: Family history questionnaire

HNPCC: Hereditary non-polyposis colorectal cancer

IBD: Inflammatory bowel disease

ICD: International Classification of Disease

IRDICC: Interdisplinary Research on the Determinants, Impact and Control of CRC

MSI: Microsatellite instability

MSI-H: High-frequency microsatellite instability

MSI-L: Low-frequency microsatellite instability

MSS: Microsatellite stable

NCTRF: Newfoundland and Labrador Cancer and Treatment Research Foundation

NCR: Newfoundland Cancer Registry

NFCCR: Newfoundland Familial Colorectal Cancer Registry

NHANES: National Health and Nutrition Examination Survey

NL: Newfoundland and Labrador

NPHS: National Population Health Survey

NSAID: Nonsteroidal anti-inflammatory drugs

ON: Ontario

OR: Odds ratio

PAR: Population attributable risk

PHQ: Personal history questionnaire

PUMF: Public Use Microdata File

RDC: Research Data Centres

RDD: Random digit dialing

RR: Relative risk

TCP: Tobacco Control Programme

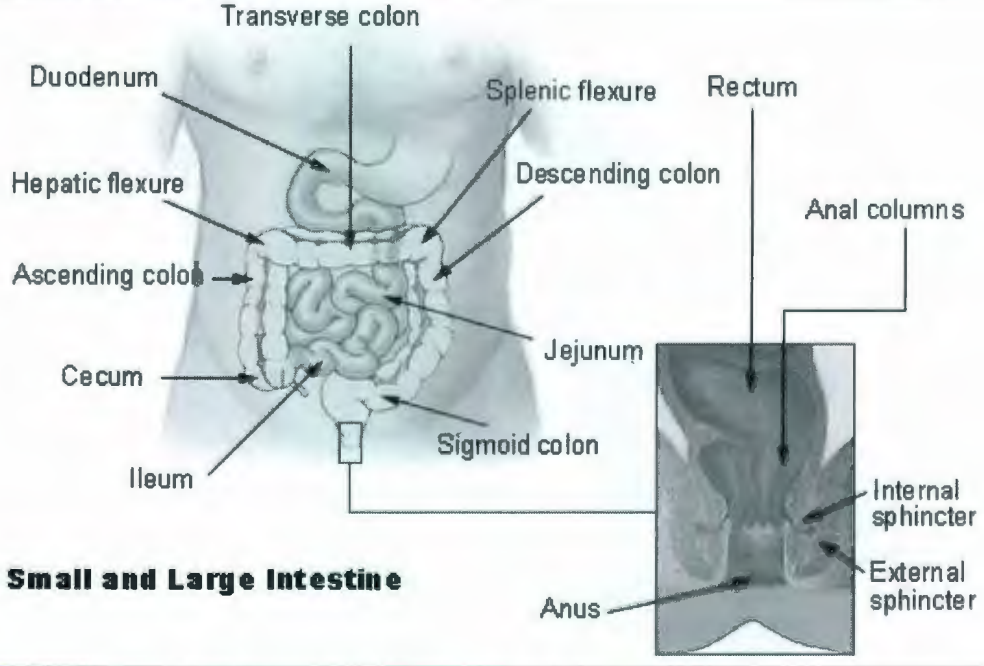
TIRCRC: Team in Interdisciplinary Research on Colorectal Cancer

Chapter 1 Introduction

1.1. Colorectal cancer

The colon and rectum make up the large intestine (large bowel, see Figure 1). The large intestine is the last part of the digestive system. The colon is the first four to five feet of the large intestine and the rectum is the last several inches [1]. The colon consists of the ascending, transverse, descending, and the sigmoid colon. The section from the cecum to the mid-transverse colon is also known as the right colon and the remainder, the left colon.

Figure 1. Diagram of the large intestine



Source: http://en.wikipedia.org/wiki/Image:Illu_intestine.jpg#file

Organs of the digestive system are responsible for converting food into energy and help pass waste out of the body [1]. Food is digested in the stomach and the small intestine. As nutrients are removed from food, it changes into a watery mass which passes on through the small intestine into the colon. The colon absorbs the water and the semi-solid waste (feces) passes to the rectum where it is stored. During a bowel movement, the feces are passed out of the body through the anus.

Colorectal cancer (CRC) is a disease originating in the epithelial cells lining the gastrointestinal tract. CRC, also called bowel cancer, includes cancerous growths in the colon, rectum and the appendix [2]. Table 1 presents the coding of CRC in the International Classification of Diseases 9th revision (ICD-9) and 10th revision (ICD-10) [3,4]. CRC usually develops slowly over a period of many years. A polyp is a growth of tissue that develops on the lining of the colon or rectum. Adenomatous polyps or adenomas are very likely to become cancers. CRC usually begins as a noncancerous polyp which may eventually become a cancerous growth. More than 95% of CRCs are adenocarcinomas which evolve from glandular tissue. In approximately 85% of CRCs, the tumour arises from an adenomatous polyp that is visible through a scope [5,6].

The majority (approximately 75%) of CRCs are sporadic, arising from somatic mutations and clonal evolution at the tumour site [7]. The remainder of cases are comprised of hereditary syndromes, i.e., familial adenomatous polyposis (FAP; 1%) and hereditary nonpolyposis colorectal cancer (HNPCC; 4-7%), family/personal history of the disease or adenomatous polyps (15-20%), or other high-risk conditions (inflammatory

bowel diseases, previous diagnoses for cancers of the ovary, endometrium, breast, bile duct, pancreas, stomach; 1%).

Table 1. Coding of colorectal cancer in the International Classification of Disease 9th revision and 10th revision

CRC	ICD-9	ICD-10
Malignant neoplasm of colon	153	C18
Caecum	153.4	C18.0
Appendix	153.5	C18.1
Ascending colon	153.6	C18.2
Hepatic flexure	153.0	C18.3
Transverse colon	153.1	C18.4
Splenic flexure	153.7	C18.5
Descending colon	153.2	C18.6
Sigmoid colon Sigmoid (flexure)	153.3	C18.7
Overlapping lesion of colon		C18.8
Colon, unspecified	153.8,153.9	C18.9
Malignant neoplasm of rectosigmoid junction	154.0	C19
Malignant neoplasm of rectum	154.1	C20
Malignant neoplasm of anus and anal canal		C21
Anus, unspecified	154.3	C21.0
Anal canal	154.2	C21.1
Cloacogenic zone		C21.2
Overlapping lesion of rectum, anus and anal canal		C21.8

1.2. Burden of colorectal cancer

1.2.1. Incidence and mortality worldwide

CRC is one of the most common neoplasm of the digestive system in the world [8]. Incidence of CRC ranks fourth in men after lung, prostate and stomach and third in women after breast and cervix uteri [8]. An estimated 1 million new cases of CRC are diagnosed every year, accounting for approximately 9.4% of total worldwide cancer cases [8]. The estimated age-standardized incidence rates of CRC were 20.1 per 100,000

in men and 14.6 per 100,000 in women in 2002 worldwide [8]. Nearly 1.2 million new cases of CRC and about 630,000 deaths from CRC occurred in 2007 worldwide according to an estimate from the American Cancer Society [9]. There is a substantial variation in global trends of the incidence of CRC [9]. The CRC incidence is increasing in certain countries such as Japan and Puerto Rico where risk was historically low. There are differential trends in CRC high risk countries with time [9]. For example, trends are gradually increasing in England, stabilizing in New Zealand, or declining in the United States. The greatest increases in the incidence of CRC appear in some Asian countries including Japan, Hong Kong and Singapore, Eastern Europe (Hungary and Poland), Israel and Puerto Rico. The recent decrease in rates has been observed in some western and northern European countries.

1.2.2. Incidence and mortality in Canada

Canada is one of the countries with the highest incidence and mortality rates of cancer in the world [9,10]. An estimated 171,000 new cases of cancer and 75,300 deaths from cancer occurred in Canada in 2009 [10]. Three types of cancer accounted for over half of the new cases in men (prostate, lung and colorectal) and women (breast, lung and colorectal) [10]. Overall, CRC is the second leading cause of cancer death for both men and women [10]. There were an estimated 22,000 new cases of CRC (12,100 in men and 9,900 in women) and 9,100 deaths from CRC (4,900 in men and 4,200 in women) in Canada in 2009. In Canada, the CRC incidence rate tended to increase, but the mortality rate of CRC decreased between 1980 and 2009 in men. The age-standardized incidence

rate for CRC increased to 62.2 per 100,000 population in 2009 from 57.9 per 100,000 population in 1980 and the age-standardized mortality rate for CRC decreased to 25.7 per 100,000 population in 2009 from 32.3 per 100,000 population in 1980 in men [10]. In women, both the age-standardized incidence and mortality rates for CRC decreased to 41.2 and 16.3 per 100,000 in 2009 from 47.4 and 25.3 per 100,000 in 1980 [10].

1.2.3. Incidence and mortality in Newfoundland and Labrador

The highest CRC incidence rates in Canada are seen among men in NL and among women in Prince Edward Island, Nova Scotia and NL; the lowest rates are in British Columbia for both sexes [10]. Mortality rates of CRC for both sexes in NL are also the highest among the provinces, and are approximately twice as high in NL as they are in British Columbia [10]. Differences in incidence or mortality rates among provinces and territories may be due to variation in the prevalence of modifiable risk factors for CRC, but there is a clear need for further work to explore this hypothesis. This thesis aims to contribute to new knowledge in this area.

1.3. Objective of the thesis

The primary objective of this thesis was to explore relations between tobacco smoking and alcohol consumption and CRC risk. The specific objectives were to (i) determine the extent of non-participation bias by comparing the differences in demographics between participants and non-participants; (ii) explore mis-reporting for

tobacco smoking and alcohol consumption using provincial sales data and the Canadian Community Health Survey Cycle 1.1 (CCHS 1.1) and Cycle 3.1 (CCHS 3.1) data for tobacco and alcohol; (iii) examine impact of tobacco smoking on CRC risk; (iv) examine impact of alcohol consumption on CRC risk.

1.4. Organization of the thesis

This thesis is divided into nine chapters. Following this short introductory chapter of the burden of CRC worldwide, the objective of this thesis and the organization of the thesis, the second chapter reviews the incidence of CRC by geographic variations, race and ethnicity and demographics; the third chapter provides a literature review of CRC risk factors explored in this thesis. The fourth chapter introduces the data sources, study design and assessment methods, and describes the statistical methods employed in this thesis. The fifth chapter addresses the first objective, the extent of potential non-participation bias by comparing the characteristics of participants and non-participants in the case and control groups in the NL population-based case-control study of CRC. The sixth chapter investigates the second objective, the reporting bias of self-reported tobacco smoking and alcohol consumption by comparing data from the case-control study with the provincial sales data of tobacco and alcohol, and self-reported data from two national surveys. The seventh chapter presents research on the third objective, the results of the relationship between tobacco smoking and CRC risk based on the database of the NL case-control study of CRC risk. The eighth chapter presents research on the fourth objective, the research results of the relationship between alcohol consumption and CRC

risk based on the database of the NL case-control study of CRC. The ninth chapter summarizes the results of this thesis and suggests future research.

Chapter 2 Socio-demographics of colorectal cancer

Research and data have showed obvious differences in the cancer incidence across populations living in different geographic areas, and populations with different socio-demographic characteristics. The purpose of this chapter is to provide an overview of geographic and socio-demographics for CRC incidence.

2.1. International and geographic variations

There is at least a 25-fold variation in occurrence of CRC worldwide [8,9]. The incidence is higher in industrialized regions such as North America, Europe and Australia than in Asia, Africa, and South America [11]. The highest incidence rates are in North America, Australia and New Zealand, Western Europe, and, in men especially, Japan. Incidence tends to be low in Africa and Asia and intermediate in southern parts of South America. The geographic distribution of colon and rectal cancer is similar, although the variation between countries is more striking for colon cancer. In high-risk populations, the ratio of colon to rectal cancer incidence is 2:1 or more. In low-risk countries, colon and rectal cancer rates are generally of the same magnitude. Significant geographic variation in CRC also exists within countries. For example, in the United States, the age-adjusted incidence rates of CRC are highest in the Middle Atlantic region, followed by New England region, East and West North Central regions, East South Central and South

Atlantic regions, West South Central and Pacific regions, with the lowest rate observed in the Mountain region [12].

The large geographic differences for colon and rectal cancers may mainly be explained by different environmental exposures. There are strong correlations internationally between risk of large bowel cancers and per capita consumption patterns of meat [13], fat [14], and fibre [15]. Epidemiologic studies have found consistent evidence that physical inactivity, excess body weight, and a central deposition of adiposity have major influences on risk of colon cancer [16]. Evidence from the study of immigrants has illustrated that the risk of colon cancer is quite labile to environmental changes; when populations moved from low-risk to high-risk areas, the incidence of CRC increased rapidly within the first generation [17,18] suggesting that dietary and other environmental factors constitute a major component of risk.

There has also been variation in CRC rates among provinces in Canada which had the highest incidence rates of CRC. Incidence rates are obviously higher in eastern provinces than western provinces, for both men and women (see Table 2). The age-standardized CRC incidence rate for males was the highest in NL and Nova Scotia, being 87 and 75 per 100,000 males and the lowest in British Columbia, being 53 per 100,000 males in 2009 [10]. The age-standardized CRC incidence rate for females was the highest in Prince Edward Island and NL, being 53 and 52 per 100,000 and the lowest in British Columbia, being 36 per 100,000 females in 2009 [10]. Provincial mortality rates had a similar pattern to incidence rates across the provinces. The age-standardized CRC mortality rate for males was the highest in NL, Prince Edward Island and Nova Scotia,

being 41, 31 and 33 per 100,000 males and the lowest in British Columbia, being 21 per 100,000 males in 2009 [10]. The age-standardized CRC mortality rate for females was the highest in NL and Prince Edward Island, being 26 and 23 per 100,000 males and the lowest in Alberta and British Columbia, being 14 and 13 per 100,000 females in 2009 [10]. While the factors that cause these real differences are not well understood, several factors including historical tobacco smoking patterns and lower socioeconomic status may be associated with the geographic variation.

Table 2. Estimated new cases and age-standardized incidence and mortality rates per 100,000 for colorectal cancer by sex among provinces and territories in Canada in 2009

Province/territory	Incidence				Mortality			
	Male		Female		Male		Female	
	N	Rate	N	Rate	N	Rate	N	Rate
Newfoundland and Labrador	290	87	200	52	130	41	100	26
Prince Edward	55	65	55	53	25	31	25	23
Nova Scotia	450	75	390	52	190	33	170	21
New Brunswick	300	64	240	40	120	25	100	15
Quebec	3,200	69	2,600	43	1,350	29	1,250	19
Ontario	4,400	60	3,700	41	1,800	24	1,500	15
Manitoba	440	65	360	42	200	30	160	17
Saskatchewan	380	63	300	40	160	26	120	15
Alberta	1,000	59	780	38	370	22	290	14
British Columbia	1,450	53	1,200	36	580	21	480	13
Canada	12,100	62	9,000	41	4,900	26	4,200	16

Source: Canadian Cancer Statistics 2009 [10].

When comparing provincial incidence and mortality with national rates from 1986 to 1996, CRC incidence rates increased significantly among men in NL [10]. Among women in Prince Edward Island, both incidence and mortality rates increased

significantly during the same period, even though these rates are based on small numbers and may be imprecise. The reasons for provincial differences in CRC incidence and mortality are not known, but may be associated with differences in exposure to modifiable risk factors such as tobacco smoking and lower intake of vegetables and fruits and genetic factors.

2.2. Race and ethnicity

The incidence of CRC varies significantly by race and ethnicity. Cancer statistics of the United States from the Centers for Disease Control and Prevention showed the incidence and mortality rates for CRC were highest in Blacks, followed by Whites, then Hispanic [19]. The incidence rate of CRC was low in American Indian/Alaska Native and Asian/Pacific Islander. Table 3 presents the age-adjusted incidence and mortality rates for CRC by races in the United States in 2006. However, other statistics found Japanese has relatively high incidence rate than other Asian people. For example, Japanese individuals born in the United States had higher rates than those of Whites in the United States in both men and women (38.4 per 100,000 in men and 27.6 in women), the rates in Japanese individuals living in Hawaii (51.2 per 100,000 in men and 30.8 in women) and Los Angeles (48.0 per 100,000 in men and 32.8 in women) were among the highest in the world [8,20].

Table 3. Estimated aged-adjusted incidence and mortality rates per 100,000 for colorectal cancer by races in the United States in 2006

Race/ethnicity	Incidence			Mortality		
	Male	Female	Total	Male	Female	Total
White	53.0	39.9	45.8	19.9	14.1	16.6
Black	63.0	49.2	54.7	30.8	20.1	24.3
Asian/Pacific Islander	40.5	31.7	35.5	12.5	9.8	11.0
American Indian/Alaska Native	34.4	26.7	30.2	13.2	9.4	11.1
Hispanic	47.3	33.2	39.3	15.3	10.8	12.8
All races	54.1	41.1	46.8	20.5	14.5	17.1

Source: United States cancer statistics: 1999-2006 incidence and mortality web-based report [19].

2.2.1. Genetics and race and ethnicity

The differences in incidence rates among various races and ethnic groups may be explained by genetic factors and environmental lifestyle factors, especially diet and exercise. Microsatellite instability (MSI) is a condition manifested by damaged DNA due to defects in the normal DNA repair process and is seen in over 85% of patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and in 15-20% of sporadic CRC patients [21,22]. Mutations in the mismatch repair genes have been found among African American patients who have either confirmed or suspected HNPCC [23].

2.2.2. Environment and race and ethnicity

Several studies have shown that migrants to the United States from Japan and other countries where rates of CRC were lower than in the United States had higher rates than those who remained in their native country. Also, first and second generation American offspring from these migrant groups developed these cancers at rates reaching

or exceeding those of the white population in the United States [24]. Further support of this observation was shown by the reduced incidence in certain religious groups such as the Mormons or Seventh Day Adventists who limit the consumption of meat, meat products, tobacco, alcohol and caffeine [25]. Jews of Eastern European descent (Ashkenazi Jews) are at increased risk of developing CRC. The observed increased incidence of CRC in Ashkenazi Jews compared to other populations was unexplained but likely had a genetic component [26-30]. This group tended to have a genetic mutation that increased the risk of developing CRC. This genetic mutation was not common among other ethnic groups.

2.3. Socio-demographic characteristics

2.3.1. Age

As with most malignancies, the development of CRC is associated with age. Statistics data have showed an increased incidence of CRC with increasing age [31-35]. In the United States, on average, one in 20 people will develop the disease in the course of a lifetime and ninety percent of cases occur in patients over age 50 [36,37]. However, recent studies have reported increased rates of CRC among younger people. For example, the proportion of African patients under 40 years with CRC was 19% in South Africa [33] and 38% of CRC occurred in patients aged younger than 40 years old in Egypt [34]. An increase in incidence rate of CRC was observed among young men and women aged 20-49 in the United States from 1992 to 2005 [38]. The aging of the body may not directly affect cancer risk, but instead it may be that the cumulative exposure to risk factors such

as tobacco smoking, alcohol consumption or cancer-causing substances with concomitant damage to DNA over time eventually leads to the disease in some individuals [39]. The high prevalence of cancer in older individuals may simply reflect prolonged exposure to carcinogens and decreasing efficiency of repair mechanisms [39].

2.3.2. Sex

In terms of incidence, CRC ranks fourth in frequency in men and third in women worldwide [8]. Studies of gender differences in CRC have shown shifts in incidence and site distribution which can be attributed, in part, to environmental and behavioral factors [40]. In high-risk populations, rectal cancer and left-sided colon cancer have been more frequent in older men, whereas right-sided colon cancer has been more commonly found in older women. Among known associations with reduced CRC risk, women appeared to ingest more dietary fibre, benefit more from physical activity, have lower body mass, and consume less alcohol [40]. Although these differences may contribute to the risk differential, hormonal events during reproductive years also appear to affect women's risk at older ages. Previous studies have found that the effect of drinking on CRC was larger for men than for women [41]. The elevated risk related to alcohol intake among men compared with women may be because of the generally lower consumption of alcohol among women; it is possible that men exhibit a greater range in the amount of alcohol drunk, which makes effects easier to detect. Also, preferred beverages may differ between the sexes, or there may be hormone-related differences in alcohol metabolism or

susceptibility to alcohol [42]. Female sex hormones are known to affect cholesterol and bile salts metabolism which in turn have been linked to the development of CRC [43].

2.3.3. Marital status

Studies conducted in developed countries found a significant relationship between CRC risk and marital status but the results tended to be inconsistent. For example, a hospital-based case-control study conducted in Italy between 1983 and 2001 found that compared to married subjects, those who have never been married were at reduced risk of cancer of the colon [44]. This Italian study showed that there was 20% and 30% lower risk of developing CRC for those who never married (OR: 0.8 and 95% CI: 0.6-0.9), or were widowed (OR: 0.7 and 95% CI: 0.8-1.0) relative to those who had married, but there was no significant difference in the risk between divorced and married subjects (OR: 1.0 and 95% CI: 0.7-1.3). Another population-based case-control study conducted in Montreal of Canada showed that subjects who had ever been married had a 42% lower risk of colon cancer (OR: 0.58 and 95% CI: 0.48-0.84) than did individuals who had never been married [45]. One analysis on the data of cancer incidence in the United States shows the highest age-adjusted incidence rates among single black men and women. The mechanism of how marital status affects CRC is unknown. The relation between marital status and cancer incidence is variable across cancer sites, calendar periods and populations [46-50].

2.3.4. Education

Years of education are generally chosen as an indicator of socioeconomic status because it, applied to every adult individual, is more stable over one's lifetime than either occupation or income [51] and is easily obtainable and recordable [52]. Variation in risk of CRC as well as other cancers by education level has been observed in epidemiological studies conducted mainly in Western countries over years. Studies seemed to show a increased risk of CRC among people who had a higher education [53-58]. A case-control study conducted in Athens, Greece in 1979-1980 showed the risk of colon cancer was increased in men with 12 years or higher education compared to no education (OR = 1.3) [53]. The hospital-based case-control study conducted in six Italian centres between 1985 and 1996 found that compared to individuals with fewer than seven years of education, the OR of colon cancer for those with 16 years education or higher was 2.45 (95% CI: 1.87-3.23) in men and 1.29 (95% CI: 0.88-1.90) in women [54]. In this study, no significant association was found between education and risk of rectal cancer [54]. Several other studies also suggested that the risk of developing CRC increased with higher education level [55-57]. Studies also showed that the risk of rectal cancer increased with higher education level [58].

2.3.5. Economic status

An increased risk of developing CRC is associated with higher economic status. Surveillance system statistics in men aged 35-64 years old in Hong Kong showed the risk of developing CRC decreased with reduced income level, i.e., the relative risk (RR) was

0.84 for medium income vs higher, 0.54 for lower vs higher, and 0.81 for lower vs medium [59]. A hospital-based case-control study conducted in 1983-1988 adjusting by sex among those under the age of 75 in Milan, Italy showed that those belonging to social class I-II (high income with UK Registrar General's social class classification) had a 1.34 times higher risk of developing CRC than social class IV-V; social class III had 1.15 times higher risk of developing CRC than social class IV-V [57]. Other studies in the United States and Sweden also showed that the risk of colon cancer decreased with a lower social class [58,60,61]. Other investigators suggest that the effects of socio-economic status on CRC vary by the subsites of CRC. For example, the study conducted in six Italian centres between 1985 and 1996 found that the OR of colon cancer was 2.30 (95% CI: 1.82-2.90) in men and 1.33 (95% CI: 1.03-1.73) in women in the highest versus the lowest social class; the study found no association between social status and rectal cancer [54]. However, other studies have shown that the risk of rectal cancer increased with higher social class [55,57,62,63].

Chapter 3 Review of genetic and environmental risk factors of developing colorectal cancer

A substantial number of cohort and case-control studies have been conducted to investigate the association of CRC and colon or rectal cancer with various modifiable lifestyle risk factors or other factors in both general populations and/or population subgroups. Many studies have found obvious differences in the cancer incidence between populations with a number of risk factors. However, many of these studies have been limited because they have not fully considered how interactions between risk factors may potentially confound or modify associations. The purpose of this chapter is to provide an overview of risk factors for CRC, concluding with a description of the rationale for the research presented in chapters 4-8.

3.1. Personal history of diseases and medications

3.1.1. Personal history of cancer

A personal history of CRC increased the risk of developing a second primary colon cancer or other cancer, particularly at the site of an anastomosis from the previous surgery [64]. Women with a history of breast, endometrial, or ovarian cancer also had an increased risk of developing CRC [65]. This might be because such patients have genetic mutations which put them at increased risk of multiple cancers. This hypothesis has been supported by evidence in a study which found women diagnosed with endometrial cancer

have mutation for inherited Lynch syndrome which puts these patients at high risk for colon as well as endometrial, ovarian and gastric cancer [66].

3.1.2. Personal history of intestinal polyps

Polyps of the colon, particularly adenomatous polyps, are a risk factor for colon cancer. Villous adenomas become cancerous up to 25% of the time, and tubular adenomas became cancerous about 5% of the time [36]. Adenomatous colonic polyps are small outgrowths from the inner lining of the colon and are different from other types of polyps that do not present an increased risk for the development of CRC. Adenomatous polyps may take from seven to twelve years to progress from normal mucosa to adenoma to cancer [36]. They are common in obese individuals and also in individuals with a high-fat consumption and in certain families. It is estimated that 19-41% of the general population will develop adenomatous polyps and about 10% of these individuals will also have a first-degree relative with a history of CRC [67]. These dysplastic adenomas are precancerous and are classified as villous, tubulovillous, or tubular. Villous lesions comprise only 10% of adenomas but are more likely to be malignant. Tubular adenomas account for 75% of adenomas but only 5% of malignancies. Patients with multiple polyps have twice the risk for cancer than those with a single polyp [67]. The overall risk of adenomatous polyps progressing to cancer has been reported as approximately 2-5%, with polyp size being a major risk factor. Polyps that are less than 0.5 mm in diameter are unlikely to progress to malignancy while those greater than 2 mm have been shown to have about a 46% malignancy rate over a 10-year interval [68].

3.1.3. Personal history of inflammatory bowel disease

Chronic inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is a condition in which the colon is inflamed over a long period of time [69]. These inflammatory bowel conditions have been associated with an increased chance of developing CRC [69]. Ulcerative colitis is a medical condition in which the inner lining of the colon becomes ulcerated in multiple places; this chronic disorder of unknown aetiology affects children and adults, with a peak incidence in the early third decade. Studies showed a significant increase in mortality from CRC among CRC patients with IBD compared with normal CRC patients [70-73]. Long duration and early onset of the disease are risk factors for CRC. The risk of Crohn's disease developing into CRC is not as high as it is for ulcerative colitis, but Crohn's disease tends to cause cancer at a younger age than in the general population.

The increased risk for developing CRC due to IBD is likely related to damage to the intestinal lining, which decreases the normal mucosal barriers that usually protect the lining [74]. Other reasons for the increased risk of developing CRC in patients with IBD could include chronic stimulation of the intestinal lining, which may lead to abnormal cell growth (dysplasia) that may progress to cancer, and the loss of enzymes that normally reduce the effect of toxins in the intestine [74].

3.1.4. Diabetes

CRC occurs more frequently in patients with type 2 (non-insulin-dependent) diabetes mellitus [75-81]. They also tend to have lower survival rates and higher recurrence

rates. The Nurse's Health Study examining the relationship between diabetes and risk of developing CRC in a cohort of 118,403 women aged 30 through 55 years who, in 1976, had not been previously diagnosed with cancer at baseline, found that diabetes mellitus conferred an increased risk of developing CRC [76]. This study showed that patients with diabetes were 1.43 (95% CI: 1.10-1.87) times more likely to develop CRC and 2.39 (95% CI: 1.46-3.92) times more likely to die of CRC than non-diabetes. Another recent study [82] which used data from the Singapore Chinese Health Study, a prospective cohort study of 61,320 Singapore Chinese men and women aged 45-74 years old, found that a history of physician-diagnosed diabetes mellitus was statistically significantly associated with CRC risk in both men (RR: 1.5 and 95% CI: 1.2-2.1) and women (RR: 1.4 and 95% CI: 1.0-1.9). People with non-insulin dependent diabetes mellitus being at a higher risk of developing CRC may be probably due to hyperinsulinemia [83] and high concentrations of insulin-like growth factor-I (IGF-I) [84,85].

3.1.5. Hypercholesterolemia

Hypercholesterolemia is a condition of a higher serum total cholesterol level which causes sclerotic changes in blood vessels, potentially leading to hypoxia of large intestine tissue and changes in the homeostasis of its cells [86]. Some studies also explored the relationship between hypercholesterolemia and CRC risk. One study which measured cholesterol levels in 7,926 Japanese-Americans for over 20 years reported an increase in serum cholesterol was associated with a decrease in risk of colon cancer, but not rectal cancer [87]. However, several other studies showed a positive relationship between serum

cholesterol levels and the risk of CRC [88-90]. It is unclear how hypercholesterolemia is associated with CRC risk. The relationship between factors causing hypercholesterolemia and factors leading to CRC development has not been fully investigated. It has been hypothesized that molecular genetic changes in normal epithelium may lead to adenomatous polyps and might result in CRC [91,92]. A recent review suggested that the increased risk of CRC associated with hypercholesterolemia may be due to relationships between the modifiable risk factors for both CRC and hypercholesterolemia [86].

3.1.6. Nonsteroidal anti-inflammatory drugs

Both cohort and case-control studies have shown that use of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with reduced CRC risks [93-97]. Furthermore, a study examining aspirin and non-aspirin-NSAID use among the initially cancer-free cohort of postmenopausal women in the Iowa Women's Health Study found that, during the 11 years of follow-up for proximal colon cancer, the multivariable-adjusted hazard ratios of proximal colon cancer for women reporting use of aspirin or non-aspirin NSAIDs two or more times weekly were 0.67 (95% CI: 0.51-0.87) and 0.71 (95% CI: 0.52-0.97) compared with nonusers of each [98]. A hospital-based case-control study reported ORs of 0.4 (95% CI: 0.2-0.8), 0.6 (95% CI: 0.4-1.0) and 0.6 (95% CI: 0.4-1.1) for proximal colon, distal colon, and rectal cancers, respectively, among recent NSAID users compared with nonusers. Another case-control study reported that, compared with nonusers, aspirin users had OR of 0.6 (95% CI: 0.5-0.8) and 0.8 (95% CI: 0.6-0.9) for proximal and distal colon cancers, respectively [99]. A cohort study found a

stronger effect of use of NSAIDs on proximal colon cancer than for distal colon or rectal cancer and the adjusted RRs among recent users with more than 12 months of cumulative use for proximal colon, distal colon, and rectal cancers were 0.48 (95% CI: 0.34-0.68), 0.77 (95% CI: 0.55-1.08) and 0.81 (95% CI: 0.49-1.32), respectively [99]. The potential anti-cancer effects of NSAIDs and aspirin may be exerted through the inhibition of COX and lipoxygenase (LOX) enzymes which play key roles in the metabolism of arachidonic acid and other polyunsaturated fatty acids.

3.1.7. Hormone replacement therapy

Several population-based case-control studies and cohort studies have found decreased risk of colon cancer among ever-users of hormone replacement therapy (HRT) in women [100-106]. The Women's Health Initiative (WHI) study conducted in the United States reported that relatively short-term use of estrogen and progestin was associated with a decreased risk (hazard ratio: 0.56 and 95% CI: 0.38-0.81) of CRC [107]. A meta-analysis of HRT and colon cancer in women showed a 15% decreased risk of colon cancer (RR: 0.85 and 95% CI: 0.73-0.99) for ever users of menopausal hormones versus non-users [108]. A recent nested case-control study showed a 66% decreased risk of CRC (OR: 0.34 and 95% CI: 0.15-0.79) among users of both oral contraception and HRT compared to non-users of both classes of hormone [109]. The inverse relationship between colon cancer and HRT may be a consequence of replacing the declining endogenous estrogen level and thus reducing the likelihood that the estrogen receptor (ER) gene may

be silenced by methylation [110]. There is evidence showing that almost all colon cancers arise in cells in which the ER gene has been silenced [111].

3.2. Family history of colorectal cancer

3.2.1. Familial risk of colorectal cancer

Approximately 16-20% of patients with CRC have a first-degree relative with CRC [112]. People who have a family history of colon cancer in first-degree relatives (parents, siblings, children) are at 2-3 fold increased risk of CRC [113-115] and colon cancer [116,117]. In some cases, the connection may not be hereditary or genetic. Instead, cancers within the same family may result from shared exposure to an environmental carcinogen (cancer-causing agent) or from diet or lifestyle factors. The likelihood ratio of colon cancer in a first-degree relative was 23.0 (95% CI: 6.4-81.0) for patients without a personal history of cancer [118]. Family history of CRC may interact with environmental risk factors of colon cancer. For example, the case-control study conducted in northern Italy between 1992 and 1996 showed that compared to subjects with no family history of CRC and in the lowest tertile of risk score of environment factors (positive family history, high education, low occupational physical activity, high daily meal frequency, low intake of fibre, low intake of calcium and low intake of β-carotene), the ORs of colon cancer was 2.27 (95% CI: 1.89-2.73) for subjects without family history and in the highest environmental risk factor score, 3.20 (95% CI: 2.05-5.01) for those with family history and low risk factor score and 7.08 (95% CI: 4.68-10.71) for those with family history high risk factor score [119].

3.2.2. Microsatellite instability of colorectal cancer

Microsatellite instability (MSI) is defined as a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumour when compared to normal tissue [120]. MSI does not describe a particular tumour phenotype but refers to the observation of instability at a given tumour. Five markers (two mononucleotide repeats and three dinucleotide repeats) are used to define and distinguish types of MSI CRC cases. CRC cases can be divided into high-frequency MSI (MSI-H) CRC cases if two or more of the five markers show instability (i.e., have insertion or deletion mutations), low-frequency MSI (MSI-L) cases if only one of the five markers show instability and microsatellite stable (MSS) cases if lacking apparent instability, i.e., none of the markers exhibit MSI. Approximately 60-70% of tumours fall into the group lacking MSI and the remaining tumours are nearly evenly split between the MSI-H and MSI-L groups [120].

3.3. Hereditary colorectal cancer syndromes

Genetic alterations play a role in the development of all colorectal malignancies. Two main genetic colorectal cancer syndromes are FAP and HNPCC [121-123] which account for 1% and 4-7% of CRC cases respectively [7].

3.3.1. Familial adenomatous polyposis

FAP is an autosomal dominantly inherited disorder marked by the emergence of hundreds to thousands of colorectal adenomatous polyps during the second or third decade of life [121-123]. Patients with this disorder have a strong predisposition for early CRC, as well as for other malignancies. In addition, several variants of the syndrome exist, namely Gardner syndrome, Turcot syndrome and attenuated adenomatous polyposis coli (APC). The incidence of FAP has been estimated to be approximately 1/10,000 and men and women are equally affected [124].

FAP is an autosomal dominant disease with almost 100% penetrance by 40 years of age [122]. Mutations in the adenomatous polyposis coli (APC) gene are responsible for the syndrome. One allele with the mutated gene is inherited from an affected parent. An acquired (somatic) mutation in the other APC allele results in the development of adenomas. However, one third of cases arise from new germline mutations in the APC gene. The absence of a family history in these cases can delay diagnosis, sometimes until after colon cancer has developed. An APC gene mutation can be identified in 87% of the patients with the disorder [125].

3.3.2. Hereditary nonpolyposis colorectal cancer

HNPCC or Lynch syndrome, is the most common form of hereditary CRC [126,127]. HNPCC is inherited in an autosomal dominant fashion. Mutations in five DNA mismatch repair (MMR) genes are currently implicated in the pathogenesis of this disorder. Fifteen

per cent to 60% of families with the clinical diagnosis of HNPCC are found to have mutations in these genes; the mutation prevalence depends on features of the family history [128]. Other less commonly implicated genes are hPMS1, hPMS2, and hMSH6. The DNA mismatch repair proteins recognize and correct small sequence errors that occur during DNA replication. Mutations in both copies of a DNA mismatch repair gene lead to the accumulation of DNA sequence errors predominantly in segments of DNA. These segments of DNA contain multiple, short, repeated sequences known as microsatellites. When these errors occur in critical growth-regulatory genes, carcinogenesis may ensue. Tumours in patients with HNPCC characteristically demonstrate microsatellite instability (MSI) - the widespread expansion or contraction of these short sequences of DNA. In HNPCC, approximately 90% of CRCs and 80% of adenomas demonstrate microsatellite instability [129].

3.4. Diet and foods

National and international studies have described associations between CRC and specific dietary habits [41,122]. The 'Western' diet, generally characterized as high in animal fat, red and processed meats, and lower in fruits, vegetables and fibre content, has been linked to an increased risk of CRC.

3.4.1. Red and processed meats

There is convincing evidence that consumption of red meats and processed meats are associated with risk of CRC [41]. 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 [41]. Ham, bacon, pastrami, salami, sausages, bratwursts, frankfurters and hot dogs are examples of processed meats.

Several cohort studies reported a significantly increased risk of CRC for the highest intake groups of red meat compared to the lowest [130-134]. Meta-analysis on seven cohort studies showed a 43% increased risk of CRC (RR: 1.43 and 95% CI: 1.05-1.94) per time/week of red meat intake and a 29% increased risk (RR: 1.29 and 95% CI: 1.04-1.60) per 100 g/day [41]. A recently published meta-analysis of 15 prospective studies further confirmed this increased risk (RR: 1.28 and 95% CI: 1.18-1.39) per 120 g/day of red meat intake [135]. The potential mechanisms for the association of CRC and red meat consumption are that high temperatures in cooking (frying, grilling, and barbecuing) red meats cause acids and creatine to react together to form heterocyclic amines [136]. Incompletely burnt meats produce polycyclic aromatic hydrocarbons [137], and gut bacteria produce N-nitroso compounds, which are potentially carcinogenic [138]. In addition, haem promotes the formation of N-nitroso compounds and also contains iron. Free iron can lead to production of free radicals and the condition of iron overload can also activate oxidative responsive transcription factors, pro-inflammatory cyctokines and iron-induced hypoxia signaling [139].

Studies showed a significantly increased risk of CRC for the highest intake group of processed meat compared to the lowest [130,140-142]. The mechanism for the association of CRC with processed meat is that preservatives added to processed meat which may contribute to N-nitroso compound production and exposure. N-nitroso compounds are suspected mutagens and carcinogens [143]. Many processed meats contain high levels of nitrites. Similar to red meat, some processed meats may be cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons.

In addition, people who consume large amounts of meat and processed meats tend to consume less poultry, fish and vegetables [41]. So it is conceivable that the relations between red meat and processed meat and CRC risk could possibly be due, at least in part, to low intakes of these other foods.

3.4.2. Fish and shellfish

High fish and shellfish intake may be associated with a decreased risk of CRC. Several studies showed significantly decreased risk of CRC for the highest intake group of fish and/or shellfish compared to the lowest [141,144]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study, which prospectively followed 478,040 men and women from 10 European countries who were free of cancer at enrolment between 1992 and 1998, found CRC was inversely associated with intake of fish, suggesting a 31% decreased risk (RR = 0.69 and 95% CI: 0.54-0.88; $P_{trend} < 0.001$) for higher than 80 g/day versus lower than 10 g/day [141]. Another study, in which 14,727 women aged 34-65 years old were enrolled at mammographic screening clinics in New

York and Florida in 1985-1991, found that there was a progressive decline in risk of CRC with increasing intake of fish and shellfish [144]. There was a 51% decreased risk of CRC for 4th quartile versus 1st quartile of fish and shellfish intake (RR: 0.49 and 95% CI: 0.27-0.89). Fish n-3 polyunsaturated fatty acids may protect against cancer [145]. Increased concentrations of short-chain fatty acids (SCFAs) and eicosanopentaenoic acid (EPA) may contribute to reduced risk of CRC [146,147] by modifying signaling pathways [148-151].

3.4.3. Foods containing animal fats

Animal fats include tallow, lard and suet, produced as part of the slaughtering process, and butter [41]. There is limited evidence suggesting that animal fat increases risk of CRC [41], but one study showed significantly increased risk of colon cancer only with increased intake of animal fats (beef, pork, or lamb) [130]. The study reported a 89% increased risk of colon cancer (RR: 1.89 and 95% CI: 1.13-3.15) for the highest quintile groups of animal fats compared to the lowest in women [130]. The potential mechanism may be because animal fats reflect the consumption of energy-dense diets, which increase the risk of obesity. Obesity influences the level of circulating leptin which has been associated with CRC [152].

3.4.4. Foods containing sugars

These is limited evidence suggesting that sugars may increase risk of CRC [41]. Foods containing sugars include refined and other added sugars, honey, fruit juices and syrups. Case-control studies showed significantly increased risk of CRC with increased intake of sugars in foods [153,154]. The study conducted in Italy showed a 43% increased

risk of CRC (OR: 1.43 and 95% CI: 1.19-1.73) for the highest versus lowest intake quintile of refined sugars [153]. The study conducted in Belgium showed a 25% increased risk of CRC among "heavy consumers of carbohydrates" compared to "light consumers of carbohydrates" [154]. Cohort studies reported a 37% increased risk of CRC for the highest versus the lowest quintile of sucrose or fructose (RR: 1.37 and 95% CI: 1.05-1.78; P = 0.008) in men [155]. Animal studies found sucrose and fructose are associated with increased colonic proliferation whereas these sugars may interfere with levels of blood glucose and/or triglycerides directly or though hormones like insulin [156].

3.4.5. Milk and dairy products

CRC risk may decrease with increased intake of milk and dairy products. There is evidence that milk probably protects against CRC [41]. Cohort studies showed a significantly decreased risk of CRC with increased intake of milk [134,157]. A recent pooled analysis from 10 cohort studies found that milk intake was related to a significant reduced risk of CRC of 0.78 (95% CI: 0.69-0.88) for the highest intake group compared to the lowest [158]. Milk may reduce CRC risk because of its calcium content. Calcium is an important micronutrient, and it has been demonstrated that intracellular calcium directly influences cell growth and apoptosis [159]. Calcium may also bind to bile and fatty acids, preventing them from damaging the intestinal lining [160].

3.4.6. Dietary calcium and calcium supplements

Calcium probably protects against CRC [41]. Both cohort and case-control studies showed that dietary calcium reduced the risk of colon cancer [161,162]. Cohort studies showed significantly decreased risk of CRC for calcium supplements compared to none [163]. Another study found a 24% decreased risk of CRC (RR: 0.76 and 95% CI: 0.56-0.98) for the highest intake group of calcium supplements compared to the lowest [164]. A pooled analysis found a 22% decreased risk for the highest intakes of dietary and supplemental sources and a larger effect for total calcium for combining dietary and supplemental sources (RR: 0.78 and 95% CI: 0.69-0.88) than for calcium from food sources (RR: 0.86 and 95% CI: 0.78-0.95) compared to the lowest intake [158]. A double-blind, placebo-controlled intervention trial showed that calcium supplementation was associated with a statistically significant 15-20% reduction in the incidence of metachronous colorectal adenomas [165]. Calcium may direct growth-restraining and differentiation- and apoptosis-inducing actions on normal and tumour colorectal cells [159]. Animal studies found that increased dietary calcium intake induced apoptosis in normal mouse distal colonic epithelium without affecting cell proliferation compared to controls [166]. This observed effect of calcium on apoptosis may result from precipitation of toxic or cytolytic fecal bile acids or fatty acids. Calcium may have an indirect effect on the colonic mucosa by precipitating bile acids and may thus inhibit their cytoxic effects [167].

3.4.7. Foods containing dietary fibre

Foods containing dietary fibre include both foods naturally containing the constituent and foods having the constituents added which probably protect against CRC [41]. Foods high in fibre include vegetables as well as grains. A combined analysis of 13 case-control studies found a reduction in CRC risk with increasing intake of dietary fibre [168]. Cohort studies showed a 25% decreased risk of CRC (Adjusted OR: 0.75 and 95% CI: 0.59-0.95) for the highest versus lowest quintile of fibre intake [169]. Meta-analysis of eight cohort studies showed a 10% reduction in the CRC risk (RR: 0.90 and 95% CI: 0.84-0.97) for intake of per 10 g/day [41]. The effect of fibre on CRC may be because fibre dilutes faecal contents, decreases transit time and/or increases stool weight [170].

3.4.8. Vegetables and fruits

There is limited evidence suggesting that non-starchy vegetables, garlic, fruits and foods naturally containing folate protect against CRC [41]. Several cohort studies showed a significantly decreased risk of CRC for the highest intake groups of non-starchy vegetables compared to the lowest [171-174]. Cohort studies have showed significantly decreased risk of CRC with increased intake of fruits [175,176]. The population-based prospective mammography screening study in women conducted in central Sweden found that total fruit and vegetable consumption was inversely associated with CRC risk and individuals who consumed fewer than 1.5 servings of fruit and vegetables per day had a RR of developing CRC of 1.65 (95% CI: 1.23-2.20) compared with individuals who consumed more than 2.5 servings [175]. A study among the elderly conducted in Japan

found no evidence of a protective effect of any dietary variables on CRC, but a reduced risk of all sites combined and of the colon for combined intake of all vegetables and fruits, fruit intake alone and dietary vitamin C [175,176].

Studies examining the relationship between vegetable and fruit consumption and colon cancer risk reported modest decreased risk in association with higher consumption [117,177,178]. Most case-control studies of colon cancer and vegetable and fruit consumption reported some degree of reduced risk with higher consumption of at least one category of vegetable or fruit [178]. Decreased risks of colon cancer have been particularly consistent for raw vegetables, green vegetables, and cruciferous vegetables. A meta-analysis of sixteen case-control studies of the relationship between vegetable intake and development of colon cancer found a combined OR of 0.48 (95% CI: 0.41-0.57) for highest versus lowest quintiles of consumption [168]. Several cohort studies also showed a statistically significant decreased effect of vegetables on the risk of developing CRC [171-174]. Cohort studies have illustrated that fruit intake significantly decreases the risk of developing CRC [176,179]. Fruits, in particular citrus fruits, are sources of vitamin C and other antioxidants such as phenols and flavonoids as well as potentially bioactive phytochemicals. Vitamin C traps free radicals and reactive oxygen molecules, protecting against oxidation damage [41]. It also regenerates other antioxidant vitamins such as vitamin E [180]. Vitamin C also inhibits the formation of carcinogens and protects DNA from mutagenic attack [181]. Beta-carotene and other carotenoid antioxidants are also found in fruits. Some fruits contain high levels of flavonoids, including apples and grapefruit. Flavonoids have antioxidant effects and can also inhibit carcinogen-activating

enzymes. Flavonoids can also alter the metabolism of other dietary agents. For instance, quercetin, directly inhibits expression of an enzyme that helps to metabolise toxins, resulting in decreased DNA damage [182]. The phytochemical antioxidants contained in fruits could reduce free-radical damage generated by inflammation. Studies reported that apples given in physiological quantities inhibited carcinogen-induced mammary cancer in rodents in a dose-response manner [183]. Fruits and vegetables may reduce risk of CRC because these foods naturally contain folate, which plays an important role in the synthesis and methylation of DNA [184]. Cohort studies that investigated dietary folate found a significantly decreased risk of CRC for the highest intake group compared to the lowest [185]. Meta-analysis showed a summary effect estimate (RR) of 0.84 (95% CI: 0.76-0.93) per 100 μg /day [185-188]. One study of serum folate levels also showed a significantly decreased risk of CRC for the highest intake group compared to the lowest [189].

Garlic is one type of allium vegetable. Studies showed significantly decreased risk for the highest consumers of garlic [190]. Preclinical evidence with model carcinogens and transplantable tumours supports an anticancer effect of garlic and some of its allyl sulphur components. Animal studies demonstrate that allyl sulphides effectively inhibit colon tumour formation and also can inhibit cell growth in the laboratory [191-194].

3.5. Lifestyle factors

3.5.1. Physical activity

Physical activity can be classified into occupational (at work), household (in the home), transportational or recreational (leisure). The evidence that physical activity of all types protects against colon cancer is convincing [41]. While three studies showed a significantly decreased risk of CRC for the highest total physical activity groups compared to the lowest [195-197], two studies observed the decreased effect of total physical activity on CRC risk in men [81,198]. Some studies showed a significantly decreased risk of colon cancer for the highest occupational activity groups compared to the lowest [199,200]. A number of studies have showed significantly decreased risk of colon cancer for the highest recreational physical activity groups compared to the lowest [81,200-205]. Studies which investigated the relationship between colon cancer and frequency of physical activity found significantly decreased risk for the highest frequency of physical activity compared to the lowest in men [81,198]. Several studies also found significantly decreased risk when comparing high with low intensity of physical activity [81,206]. It has been estimated that physical activity of two hours or more per week can significantly reduce the risk of developing CRC [85]. Individuals with high levels of activity throughout their lives were found to have the lowest risk [117,178]. Inactivity tends to slow the speed at which food contents pass through the colon and may also cause constipation, both of which increase the length of time the colon lining is exposed to colonic contents. There are a number of other mechanisms by which physical activity may protect against CRC. These include a reduction in insulin resistance, the beneficial effect of physical activity on body fatness, as well as reduced gut transit time [207,208].

3.5.2. Body fatness

The evidence that greater body fatness and abdominal (central) fatness are associated risk of CRC is convincing [41,206]. Body fatness is commonly estimated using the body mass index (BMI), a measure of weight adjusted for height and is calculated as weight in kilograms divided by height in metres squared (kg/m^2) [209]. Many cohort studies showed a significantly increased risk of CRC with increased body fatness [41]. Meta-analysis of 28 cohort studies showed a 3% increased risk of CRC (RR: 1.03 and 95% CI: 1.02-1.04) with one unit increase of BMI and a larger effect on rectal than colon cancer [41]. A report published in 2002 by IARC evaluated all available studies on obesity (BMI>30 kg/m^2) and CRC risk and found that obesity increased CRC risk and elevated risks in men and women with risks being stronger for men than women [210]. Cohort studies show that there was about a 50-100% higher risk in the highest quartile of BMI compared to with the lowest quartile [210]. Although BMI is a commonly used proxy for fatness, it does not reflect how fat is distributed in the body and it has also been criticized for not accounting for muscle mass. Thus some studies have examined the impact of waist circumference as a proxy for abdominal fatness, on risk of CRC. Several studies showed a significantly increased risk of CRC with increased waist circumference [204,211-214]. Meta-analysis on four cohort studies showed a 5% increased risk of CRC (RR: 1.05 and 95% CI: 1.03-1.07) per 2.5 cm (1 inch) increase of waist circumference [41]. Some studies found increased risk of CRC with increased waist to hip ratio [204,211-215]; meta-analysis on five cohort studies showed a 30% increased risk of CRC (RR: 1.30 and 95%

CI: 1.17-1.44) with 0.1 increment of waist to hip ratio [41]. There is evidence to suggest that waist to hip ratio (WHR) appears to be superior indicators of obesity than BMI. One recent study conducted among men reported a 2.1-fold increased risk of colon cancer for men comparing a high WHR to those with a low WHR, whereas a high BMI (>29.2 kg/m^2) conferred a 1.7-fold increased risk of colon cancer compared to a BMI<24.8 kg/m^2 [216]. One prospective study found a 2-fold elevated risk for CRC among men and women with a waist size greater than 99.1 cm compared to a waist size less than 83.8 cm [212]. There are several potential mechanisms by which body fatness may increase the risk of CRC. Abdominal fatness increases the level of insulin resistance and the pancreas compensates by increasing insulin production which increases the risk of colon cancer [207]. Obesity is characterized by a low-grade chronic inflammatory state [217]. Adipocytes produce pro-inflammatory factors and obese individuals have elevated concentrations of circulating tumour necrosis factor (TNF)-alpha [218], interleukin (IL)-6 and C-reactive protein compared with lean people [219], as well as of leptin which also functions as an inflammatory cytokine [220]. Chronic inflammation can result in DNA damage and cancer promotion because a chronic inflammatory environment can increase proliferation and differentiation, inhibit apoptosis and induce angiogenesis [221].

3.5.3. Adult attained height

The evidence that the factors that lead to greater adult attained height increase the risk of CRC is convincing [41]. Cohort studies showed significantly increased risk of CRC with increased attained height [200,204,222-225]. Meta-analysis of 12 cohort studies reported a

9% increased risk of CRC (RR: 1.09 and 95% CI: 1.06-1.12) per 5 cm increase in height [41]. Adult height is unlikely to directly modify the risk of CRC. It is a marker for genetic, environmental, hormonal and nutritional factors which affect growth during the period from preconception [41].

3.5.4. Tobacco smoking

A total of 60 epidemiological studies have reported an relationship between tobacco smoking and CRC in the last three decades, but few were specifically designed to study the effects of tobacco smoking, and only a few found a significantly increased risk for CRC among smokers. Of 16 prospective cohort studies conducted in the United States, 10 in Europe and three in Japan, most showed a small elevated risk for colon cancer, rectal cancer or CRC among smokers. Only a few studies showed that former and/or current smokers exhibit a significantly increased risk of 1.2-1.4 for colon cancer [226,227], rectal cancer [226-230] or CRC [198,231,232], relative to those who have never smoked. Of all cohort studies, one showed a statistically significantly decreased risk among smokers [233].

Many case–control studies which examined the association between active smoking and cancer of the colon and rectum were conducted in European countries [234-242], in Asia [243-252] and in the United States [58,253-259]. Of these case–control studies, only a few showed statistically significant increased risk among former or current smokers or ever-smokers [255,257,260]. There are studies reporting a statistically significant reduction in risk for cancer of the colon [246] and rectum among smokers [261].

A dose-response relationship between smoking and CRC has been identified in some studies, but the association seems to be inconsistent by subgroups such as subsites of CRC and gender. Several cohort studies reported statistically significant dose-response trends with amount smoked daily for colon cancer [226,227], rectal cancer [226,227,229] and CRC [231,232]. Some case-control studies have also shown a statistically significant positive trend of increasing risk with increasing number of cigarettes smoked daily for colon cancer [256,257], rectal cancer [256] and CRC [250]. In another two studies, this pattern of increasing risk was apparent only in men [252,255] but not among women in the same study. However, the relationship between CRC and amount of smoking is somewhat inconsistent. For example, studies showed a statistically significant trend of increasing risk with increasing pack years of smoking [227,231,232], but another study indicated this association was limited to those who started smoking before the age of 30 years [262].

The relationship between smoking and the risk of colon and rectal cancer was investigated separately in the majority of previous cohort and case-control studies and risk patterns are generally consistent between colon and rectal cancer in these studies [263]. However, some studies found inconsistent results of the relationship between subsites of CRC and smoking. While several studies showed the effect of smoking was more apparent for rectal cancer than for colon cancer [246-249,256,264], a few studies reported a stronger effect of smoking on colon cancer than rectal cancer [265,266].

Several previous studies, which explored the relationship between cigarette smoking and microsatellite unstable colon cancer or CRC provide inconsistent results. one case-control study found that cigarette smoking was associated with MSI-H CRC [267].

One case-control study conducted in the United States found that cigarette smoking increased the risk of both colon cancer with MSI-positive and MSI-negative compared to controls, but the risk was significantly higher for MSI-positive tumour than MSI-negative tumour [268]. Another case-control study also found that the risk of MSI-positive CRC was increased in patients who smoked [269], but other could not confirm this [270].

Previous studies by gender are somewhat inconsistent. Several cohort studies have reported that the association between smoking and CRC is stronger in men than in women [198,228,271]. However, one study reported a significantly increased risk associated with smoking only in women and not in men [272] and another showed the association between smoking and CRC was equally strong in both sexes [231]. While two case-control studies showed smoking was a risk factor only in men [252,255], three showed no clear gender differences [257-259]. This thesis found the effect to be stronger among males than females.

In some studies, drinking alcohol is considered as a confounder of the relationship between CRC and smoking and its potential confounding effect is adjusted for [226,265,273,274]. Few studies have evaluated whether the association between smoking and CRC was modified by alcohol consumption even though in a study that examined the joint effect of smoking and drinking, a significant increase in risk of polyps was found only among subjects who were both smokers and drinkers [275].

Several studies examined the combined effects of smoking and body weight on colon or rectal cancer [256,257]. One study which investigated whether the association between smoking and CRC was modified by body weight found the risk of rectal cancer

was significantly greater among heavier women [256]. Another study found that smokers with a high BMI displayed higher risk of colon cancer than those with a lower BMI [257].

There are methodological weaknesses in many previous studies. Inadequate adjustment for various potential confounders (e.g. alcohol, physical activity, body size, dietary factors) or unidentified confounders could account for the small increase in risk found with smoking in some studies. For example, smokers are more likely than non-smokers to be physically inactive [276], to use alcohol, to have poorer dietary habits (e.g. lower consumption of fruits and vegetables and higher consumption of fat and meat) and they are less likely to be screened for CRC [277]. Each of these factors, in turn, is positively associated with CRC risk [117]. Thus, if these potential confounders are inadequately controlled for or not controlled for in the analysis, then smoking may appear to increase the risk for CRC even if it has no direct effect on risk. A few potential confounders were adjusted for in most of the cohort studies. One third of the published studies considered only age or other relevant demographic factors [117,226,227,231,271,278-282]. Some studies adjusted only for demographic factors and alcohol use [226,265,274]. Less than half of the studies considered two or more of the potential confounders mentioned above [198,206,227,231,232,262,266,281-286]. The extent to which residual effects of potential confounders can explain the small increase in risk associated with smoking cannot be determined for certain. In some studies, adjustment for alcohol [273] and other risk factors [262] substantially reduced the magnitude and the significance of the effect of smoking. In other studies, the risk estimate associated with smoking was reduced by up to 10% although the association remained statistically significant [231,232]. None of the prospective

studies has evaluated whether the association between smoking and CRC was modified by other characteristics such as alcohol intake, body weight, and others. In about half of the case–control studies, demographic factors and at least two of the potential confounders discussed above were adjusted for in the analyses [236,237,240,242,250,251,255-259,264,287,288]. Few studies have examined the association of tobacco smoking with other factors such as obesity and alcohol intake on CRC.

3.5.5. Alcohol intake

In 1957, Stocks first reported a marginally elevated risk of developing CRC among daily beer drinkers compared with abstainers [289]. Subsequently, this association with cancers of the large bowel has been explored in other studies. The measures of alcohol drinks include the number of alcoholic drinks per time period and ethanol intake in grams or milliliters per time period. The number of drinks is less likely to be precise because the size and strength of each drink is unknown. However, previous studies showed increased risk of CRC with increased consumption of total drinks and ethanol. For example, some studies found significantly increased risk of CRC for the highest intake group of total alcohol drinks compared to the lowest [249,273,290,291]. Several other studies showed significantly increased risk of CRC for the highest intake group of ethanol compared to the lowest [198,200,226,249,292-294].

Some studies investigated the association of subsite of CRC with types of beverage. For example, the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-Up Study (NHEFS) which includes a prospective

cohort population representative of the general United States population which consisted of 10,220 participants prospectively followed over a decade, showed that the consumption of one or more alcoholic beverages a day at baseline was associated with approximately 70% greater risk of colon cancer (RR: 1.69 and 95% CI: 1.03-2.79), with a strong positive dose-response relationship [295]. This association appeared to be exclusively related to daily drinking of one or more drinks of liquor (RR: 2.48 and 95% CI: 1.66-4.53). Additionally, an increased risk of 73% was observed for more than 34 years of alcohol drinking history compared with nondrinkers (RR: 1.73 and 95% CI: 1.08-2.78). Other studies found that consuming more than seven alcoholic drinks a week increased the risk of developing CRC by 72% [296]. Pooled analysis of primary data from eight cohort studies in five countries in North America and Europe, which consisted of 489,979 women and men with no history of cancer other than non-melanoma skin cancer at baseline, found that increased risk for CRC was limited to persons with an alcohol intake of 30 g/d or greater [297]. Compared with nondrinkers, the pooled multivariate relative risks were 1.16 (95% CI: 0.99-1.36) for persons who consumed 30-44 g/d and 1.41 (95% CI: 1.16-1.72) for those who consumed 45 g/d or greater [297]. However, the epidemiologic findings on the relationship between alcohol consumption and CRC are inconsistent. Many studies have not reported any statistically significant increased effects of alcohol intake on CRC. For example, among twenty cohort studies reporting marginally increased risk for the highest intake group of total alcoholic drinks when compared to the lowest [171,186,187,199,204,214,249,265,273,283,290,298-306], only four studies showed a statistically significant increase [249,273,290,291]. Two studies reported no effect on risk [307]

and three studies reported decreased risk; none was statistically significant [292,308-311]. The inconsistencies may be the consequence of small sample sizes, differences in control groups or study methods, or differences in preferred beverages between the sexes and across countries. These inconsistencies could also be possibly due to population differences in susceptibility to, and metabolism of, alcohol.

Several studies showed that the effects of alcohol consumption on CRC risk varied by subsite of CRC and MSI status [312]. When comparing MSI+ to MSI- tumours this study observed that long-term alcohol consumption increased the probability of having a tumour with MSI (OR for MSI-positive vs. MSI-negative colon cancer for alcohol: 1.6 and 95% CI: 1.0-2.5). The likelihood of having MSI in the tumour from the combined effects of high alcohol consumption and smoking cigarettes showed a 70% excess in risk from the additive model [312].

3.6. Research questions

In general, CRC has been considered an outcome of interactions between several genetic and environmental factors. However, studies exploring the relationships between CRC and some of these factors have been inconclusive. This thesis focuses on the relationship between CRC and tobacco smoking and alcohol consumption. The primary analysis was based on the data in the Newfoundland and Labrador population-based case-control study of CRC and the relevant methodological issues also constitute one component of this thesis. Four specific objectives in this thesis are: (a) assessing non-participation bias; (b) assessing reporting bias of lifetime tobacco smoking and alcohol

consumption; (c) investigating the effects of tobacco smoking on CRC incidence; (d) investigating the effects of alcohol intake on CRC incidence.

3.6.1. Non-participation bias of cases and controls

A trend of decreasing response rates in population surveys is a growing concern in epidemiological research due to the increased likelihood of non-response bias [313]. Low response rates may compromise the generalizability of population survey data [314], especially when the percentage of non-respondents is large and when non-respondents differ greatly from respondents [315]. Non-response is an important source of inaccurate reporting of alcohol and illicit drug use in population surveys [313,316]. The resulting underestimates of consumption could change the association between risk variables and prevalence [313]. Unfortunately, non-response bias is usually difficult to determine because researchers rarely have information about non-respondents. Few studies on non-response bias in surveys in the alcohol and drug field have provided a clear answer to the issues raised. While some studies found no significant non-response bias in estimating population attributes [317-319], others indicated that bias exists [320] and there is a serious chance of bias when a response rate is below 70 percent [321]. The degree of non-response bias is likely related to the focus of the study [320]. Several studies about direction of non-response bias in surveys provide conflicting results. Some studies showed that non-participants were more likely to abstain from alcohol than participants [322,323], whereas others indicated non-participants were more likely to drink and were more likely to be heavier drinkers than participants [324]. In the population-based case-control study of CRC

conducted in NL, of 1,171 eligible CRC cases, 702 completed and returned the questionnaires, a participation rate of 60%. Of 1,602 controls of meeting eligibility criteria, 717 completed questionnaires were returned and the participation rate was 45%. Therefore, non-participation is the main source of potential bias for assessing exposure to risk factors for developing CRC such as cigarette smoking and alcohol use in this population. One of the objectives of the analyses presented in this thesis was to assess the extent and direction of non-response bias operating in the NL population-based case-control study of CRC and the degree of its impact on prevalence estimates reported to date.

3.6.2. Reporting bias of tobacco smoking and alcohol consumption

The population-based case-control study of CRC conducted among NL residents to investigate the relationship between developing CRC, tobacco smoking and alcohol intake were based on self-reporting of participants. It is a concern, especially in the context of case-control studies, when cases and controls are asked about exposure in the past. Recall bias is a possibility in any case-control study that uses an anamnestic response, since the cases and controls, by definition, are people who differ with respect to their disease experience and this difference may affect recall [325]. The accuracy of recall is usually related to the amount of time elapsed between the exposure and the recall [326]. Lifetime measures might be inaccurate because of the concern about the accuracy of long-term recall after 18 years [327]. For a variety of reasons, including issues of social desirability or sensitivity, subjects may not be willing to report an exposure accurately. When researchers gather baseline characteristic data, subjects may underestimate the

number of cigarettes they smoke or amount of alcohol they drink [328]. Errors in recall of these past exposures result in misclassification of exposure status, thus biasing the results of the study. If the recall error differs between cases and controls, the misclassification is said to be differential; if the recall error is of similar magnitude, the error is said to be non-differential. Recall bias resulting from inaccurate recall of past exposure is perhaps the most often cited type of exposure identification bias.

The bias caused by differential misclassification can either exaggerate or underestimate an effect [325]. Differential misclassification bias can lead either to an apparent association even if one does not really exist or to an apparent lack of association when one does exist [328]. If the true RR or OR is close to 1.0, a non-differential misclassification may completely mask the association. Lifetime measures of alcohol consumption have been available for as much as a quarter century [329]. Several studies have found substantial discrepancies between alcohol consumption estimates based on survey data and those derived from sales data. Per capita consumption estimates derived from survey-generated self-reports of drinking behaviours have tended to yield estimates of per capita consumption at between 40% and 60% of the results obtained from sales data [330]. Lifetime alcohol drinking and tobacco smoking have been used to investigate the effect of alcohol consumption on chronic conditions such as cancer in case-control studies. However, few studies have been conducted to investigate the accuracy of self-reporting lifetime alcohol intake and tobacco smoking.

3.6.3. Tobacco smoking and colorectal cancer

While previous studies showed that incidence of CRC has been associated with lifestyle risk factors including dietary factors [331,332], and physical inactivity [204], studies on the relationship between CRC and tobacco use have been conflicting. Studies that found an association of CRC incidence with tobacco smoking showed that development of CRC might have been associated with specific types of tobaccos. For example, some studies found greater risk of developing CRC associated with smoking cigars and pipes but not smoking cigarettes [255,333,334]. Tobacco smoking might also affect subsites of the bowel. A study conducted in Hong Kong showed that cigarette smoking was related to rectal cancer risk but not to colon cancer risk [335], but several studies have also shown a higher risk for colon cancer among cigarette smokers, especially among those with very long smoking histories [336-338]. The effect of tobacco use on CRC in the Canadian population may differ from that in other countries because Canadian tobacco brands and hence tobacco composition, may differ from those in other countries [339,340]. In Canada, only one study specifically on tobacco smoking and CRC has been carried out. This Montreal study did not provide any evidence for an association between tobacco smoking and CRC [339] but cannot be generalized to other provinces such as NL where the population shows different lifestyle and genetic characteristics [257,340-342]. Therefore, to explore whether tobacco use is associated with the risk for CRC, whether different tobacco types influence risk differently, and whether tobacco is associated with cancer in specific parts of the bowel and whether other characteristics such as sex, survival status,

familial risk, drinking status, obesity and microsatellite instability (MSI) influence risk, further studies on the relationship between tobacco smoking and CRC are required.

3.6.4. Alcohol consumption and colorectal cancer

As described in Section 3.5.5., there are some limitations in studies that have previously examined relationship between CRC risk and alcohol consumption. For example, some studies included only one measure of alcohol consumption at baseline and could not investigate lifetime alcohol consumption, alcohol consumption at younger ages, or changes in alcohol consumption during follow-up [297]. A further issue is whether the effects reported elsewhere can be demonstrated in Canada since almost all studies have been conducted in other countries and the alcohol content in alcoholic beverages made in Canada differs from that in other countries [343]. Canada has had the highest incidence rate of CRC in the world and NL has had the highest incidence rate in the country [9,342]. However, only one study on alcohol and CRC incidence has been carried out in Canada and that was done among men in Montreal, Quebec. The findings of this study cannot be generalized to other Canadian populations such as NL. One reason is that the relatively isolated community of NL exhibits different lifestyle and genetic characteristics from those observed in other parts of Canada [344]. For example, alcohol drinking or heavy drinking prevalence is higher in NL than in other Canadian provinces [345,346], but no studies have been conducted to investigate the effect of alcohol intake on CRC in the general population and subgroups in NL. Studies conducted in other populations showed that cigarette smoking [41,263] and obesity [347] may play a role in increasing CRC risk.

Historically, there has been a relatively high prevalence of tobacco use in NL [348-350], and the province also has the highest prevalence of obesity in men and women (33.3% and 34.5%) when compared with the prevalence reported for Canada as a whole [350]. However, there are no reports in the literature to investigate the combined effects of alcohol consumption, cigarette smoking and obesity on CRC risk.

Further studies need to be conducted in this population to explore whether or not alcohol intake is associated with the risk of developing CRC, whether different alcoholic beverages influence risk differently, and whether alcohol is associated with cancer in particular parts of the bowel and whether other characteristics such as sex, survival status, familial risk, smoking status, obesity and microsatellite instability (MSI) influence risk.

Chapter 4 Research methods

4.1. Data sources

This thesis is based on several data sources: a) data from population-based case-control study of CRC in NL; b) data of the CCHS 1.1 and CCHS 3.1; c) sales data of alcoholic beverages; d) wholesale sales data of tobacco; and e) Statistics Canada population data. The study on the relationship between tobacco smoking and alcohol consumption and CRC, as well as the study on non-participation bias, were based on the data of the case-control study of CRC, which included the demographic and clinical information of 1,171 eligible CRC cases identified from the Newfoundland Cancer Registry (NCR) who consented to participate in the study of CRC, and the demographic information of 1,602 eligible controls randomly selected from the NL population who consented to participate in the study of CRC. The analyses on the bias of self-reported tobacco smoking and alcohol consumption was based on the data of the case-control study, data concerning tobacco and alcohol sales, population data obtained from Statistics Canada and Health Canada, and data of the two cross-sectional surveys, CCHS 1.1 and 3.1, obtained from Statistics Canada.

4.1.1. Data of the case-control study of colorectal cancer

4.1.1.1. Introduction to the case-control study

Case-control studies are particularly useful in the evaluation of potential risk factors for diseases of long latency such as cancer [351,352]. The major strengths of a case-control study are that it can simultaneously evaluate many causal hypotheses, permit the evaluation of interaction in which two or more causes of the disease modify the strength of one another, permit the evaluation and control of confounding, and contribute rich information compared to a cohort study because of the large number of ill persons observed in a case-control study [353]. Additionally, case-control studies are often a relatively inexpensive type of epidemiological study, usually conducted by small teams or individual researchers in single facilities. They can be done in less time and require fewer participants than prospective studies. The current thesis, which explores the relationship between CRC and tobacco smoking and alcohol consumption in NL, is a component of a large study on CRC conducted in NL and Ontario (ON) by the Canadian Institute of Health Research Team in Interdisciplinary Research on Colorectal Cancer (TIRCRC, Principal Investigator: John R. McLaughlin) which consists of health researchers throughout the provinces of ON and NL who are conducting serial linked CRC studies that involve a wide range of scientific disciplines (details on the project at: http://www.mshri.on.ca/colorectalcancer/). The design was used to identify risk factors, including tobacco smoking and alcohol consumption, which may contribute to

developing CRC by comparing the exposures in a group randomly selected from the NL population who had not had CRC when selected (see Figure 2).

The NL population-based case-control study of CRC collected information on tobacco smoking and alcohol consumption, and relevant epidemiological factors from cases and controls and blood samples from CRC cases. The database of the case-control study also stored demographics of all eligible cases identified in NCR and consenting, participating controls were selected randomly from the NL population. Eligible cases were NL residents between 20 and 74 years old, diagnosed with CRC between 1999 and 2003, with histologically confirmed primary adenocarcinoma of the colon or rectum. Controls were randomly selected from the general population within the same five year range and sex as cases. Population controls were contacted by telephone using random digit dialing (RDD). Data collection was performed under the auspices of the Clinical Epidemiology Unit and Health Research Unit of Memorial University of Newfoundland. The study was under the supervision of the two principal investigators (Patrick Parfrey and Ban Younghusband). Telephone interviews were also adapted, given the literacy level of certain parts of the population. In rare instances, when telephone contact could not be made, data were collected with personal interview. A detailed description of the recruitment of controls has been reported elsewhere [354].

4.1.1.2. Ethics review of this thesis

The study is one component of the Interdisciplinary Research on the Determinants, Impact and Control of Colorectal Cancer (IRDICC), a population-based study in ON and

NL funded by the Canadian Institute for Health Research (the principal investigator: John Ross McLaughlin; the period from: 2006-04-01 to: 2011-03-31). The Ethics Review Board of the Memorial University of Newfoundland approved this study [see Appendix I: The letter of ethics approval from the Memorial University Human Investigation Committee (HIC 01.70)]. The database includes all relevant data in the proposed study of tobacco and alcohol and CRC in NL population. The self-administered questionnaires for data collection of tobacco smoking and alcohol consumption and other epidemiological variables previously used are attached (Appendix II). The primary study includes 702 CRC patients who were diagnosed in the NL population between 1999 and 2003 and 717 controls randomly selected from NL population during the period of the cases diagnosed. No participants were contacted by the author for any further information. The case and control database were obtained from the supervisor of the author, Dr. Peizhong Peter Wang who is conducting the epidemiological study of genetic and environmental factors of CRC based on the data requested as one of principal investigators (see Appendix III).

This thesis also analyzed sale data of tobacco (Appendix IV and V), sales data of alcohol beverages (Appendix VI and VII), population data (Appendix V and VII), and the data of the CCHS 1.1 and CCHS 3.1 in the assessment of the accuracy of self-reported alcohol consumption and tobacco smoking in the NL case-control study of CRC. While these data can be obtained though the websites of Health Canada and Statistics Canada or through the Research Data Centres of Statistics Canada, and no human subjects were involved, this thesis utilized these datasets in which individuals cannot be identified, and as a result an ethical review was not required.

4.1.2. Sales data of tobacco and alcohol and population data

4.1.2.1. Sales data of tobacco

The sales data of tobacco were obtained from the Cigarette and Fine-Cut (cut up into shreds) Sales Charts 1980-2008 of Health Canada [348]; this data can be reviewed in Appendix IV. Health Canada through its Tobacco Control Programme (TCP) provides relevant and timely information to support decision making and development of effective anti-tobacco policies and programs. The TCP monitors and analyzes changes in tobacco consumption patterns, public attitudes, retailer behaviour to youth access restrictions, industry practices and the product in support of TCP's programs and mandate. The sales data are provided to Health Canada by manufacturers and importers of tobacco products. The provision of this data to Health Canada is mandatory under Section 13 of the Federal Tobacco Reporting Regulations. Cigarette and fine-cut tobacco sales data are provided monthly by the companies to Health Canada (received by the 15th of every month for the previous month). Once received, the data are examined completeness and accuracy. Once the completeness and accuracy of the data are determined, the data is entered into Health Canada wholesale sales database. The data for cigarettes and fine-cut provide a very accurate national picture of legal, wholesale cigarette and fine-cut sales. Annual totals for the previous year are published on the website once a year (usually posted mid-year for the previous year). These reports are available nationally and provincially for wholesale tobacco sales since 1980.

4.1.2.2. Sales data of alcoholic beverages

The sales data of alcohol beverages in NL were obtained from Statistics Canada [355], and can be reviewed in Appendix VI. The Public Sector Statistical Program of Statistics Canada is a component of the Canadian System of National Accounts and collects data from the provincial and territorial government liquor authorities on the value and volume of sales of alcoholic beverages, and on financial information. The information is used by governments, by the liquor, wine and beer industries, international agencies and researchers.

The target population consists of all provincial and territorial government liquor authorities. Data are collected for all units of the target population; therefore, no sampling is done. Response to the survey is mandatory and data are collected directly from survey respondents, extracted from administrative files and derived from other Statistics Canada surveys and/or other sources. Data are collected directly from provincial and territorial government liquor authorities and complemented with data extracted from administrative files. Additional data are also provided by the International Trade Division of Statistics Canada. Minimal error detection procedures are used to minimize errors. Imputation is performed for certain information not provided, and non-response. Analysis, review and cross-checking ensure high quality data. Volume of sales of alcoholic beverages in litres of absolute alcohol is calculated by multiplying the sales volume by the percentage of alcohol content. The conversion rate was 5% for beer, 11.5% for wine and 40% for spirit [346,355].

4.1.2.3. Population data

This thesis needs the population data to calculate annual per capita alcohol and tobacco use and create the weighting variable to estimate annual per capita alcohol and tobacco use based on the sample of controls in the case-control study. The population data were obtained from Statistics Canada [356]. The estimates program of population in Statistics Canada provides annual estimates of population by age and sex for Canada, provinces and territories. The estimates program is used in the calculation of demographics, social and economic indicators in which the population or part thereof, serves as the denominator. These data are used in calculation of weights for use in Statistics Canada's Surveys.

The population universe covered by the Demographic Estimates Program is similar to the population universe of the Census. Post-censal estimates are obtained by the component method, using the most recent census of population adjusted to July 1, and for net census undercount (the number of people missed by a census who were meant to be counted) as the base population. The component method consists in taking the population figures from the most recent census, adjusted for census net undercoverage, and adding or subtracting the number of births, deaths, and components of international and interprovincial migration. Annual population for each five year age group for NL was extracted from the Demographic Estimates Program and population aged 20-74 for NL was calculated by summing estimates of population of each age group to obtain an estimate of the population aged 20-74 in NL. Annual population aged 20-74 in NL can be reviewed in Appendix V and VII.

4.1.3. National health survey data

The data of the CCHS 1.1 and CCHS 3.1 were analyzed and compared with the case-control study data to examine any differences in patterns of self-reported drinking and smoking in Canadians between the case-control study and the CCHS. The CCHS is a cross-sectional survey that collects information related to health status, health care utilization and health determinants for the Canadian population. It relies upon a large sample of respondents and is designed to provide reliable estimates at the health region level. The objectives of the CCHS are to support health surveillance programs by providing health data at the national, provincial and sub-provincial levels; provide a single data source for health research on small populations and rare characteristics; and to create a flexible survey instrument that includes a rapid response option to address emerging issues related to the health of the population. Data are available for the 2001, 2003 and 2005 periods. However, the data in 2001 and 2005 were selected for the comparison of the estimates and patterns of alcohol use and smoking with the case-control study data.

4.1.3.1. Canadian Community Health Survey Cycle 1.1

The analysis was based on data collected from September 2000 to November 2001 from the first cycle of the CCHS [357]. The data and relevant information on the CCHS can be obtained through the Research Data Centre of Statistics Canada. The CCHS 1.1 covered approximately 98% of the Canadian population aged 12 or older. The

CCHS 1.1 questionnaire was administered using computer-assisted interviewing (CAI). Sample units selected from the area frame were interviewed using the Computer-Assisted Personal Interviewing (CAPI) method, while units selected from the RDD and telephone list frames were interviewed using the Computer-Assisted Telephone Interviewing (CATI) method. The area frame, as designed for the Labour Force Survey (LFS), uses a multistage stratified cluster design [358]. A complete description of the LFS area frame is given elsewhere [359]. At the Canada level, the response rate was 84.7% for the CCHS 1.1 sample which consists of 139,827 individuals. The response rate was 86.8% in NL. The NL sample consists of 3,870 respondents aged 12 years and older. CCHS 1.1 collects data in all health regions of the province. The analyses undertaken for this thesis include a total of 3,017 respondents aged 20-74 years old in NL.

4.1.3.2. Canadian Community Health Survey Cycle 3.1

The Public Use Microdata File (PUMF) contains data collected for CCHS Cycle 3.1 between January 2005 and December 2005 [360]. The CCHS 3.1 collects responses from persons aged 12 or older, living in private occupied dwellings in 122 health regions covering all ten provinces and one health region per territory, totaling 125 health regions. Excluded from the sampling frame are individuals living on Indian Reserves and on Crown Lands, institutional residents, full-time members of the Canadian Forces, and residents of certain remote regions. The CCHS covers approximately 98% of the Canadian population aged 12 and over. At the Canadian level, the response rate was 78.9% for the CCHS 3.1 sample which consists of 132,947 individuals. The response rate

was 85.7% in NL, consisting of 4,111 respondents aged 12 years and older. CCHS 3.1 collects data in all health regions of the province. The analyses described in this thesis include 3,239 respondents aged 20-74 years old in NL.

4.2. Case-control study of colorectal cancer

4.2.1. Case and control identification

4.2.1.1. Case identification

Eligible CRC cases were NL residents between 20 and 74 years old, newly-diagnosed with CRC between January 1999 and December 2003, with histologically confirmed primary adenocarcinoma of the colon or rectum. Records of the NCR were reviewed to identify cases and pathology reports were sought to confirm the diagnosis. Pathology reports retrieved by the NCTRF from provincial pathology laboratories were reviewed by the study pathologist. The recruitment and survey of cases were carried out during the period between November 2001 and April 2006. Eligible cases were then contacted through their attending or family physician to inform them of the study. Eligible cases indicated their willingness to participate by informing their attending physician through calling a 1-800 number, or by responding to a follow-up phone call from NCTRF staff. There were a total of 1,664 newly-diagnosed cases of CRC in NL during the period from 1999 to 2003 [377]. A total of 1,171 CRC cases diagnosed in 1999-2003 which accounted for 84.8% of all eligible cases (1,388) [377] were considered to be eligible and consented to participate in the study. Table 4 presents the number and

percentage of these new CRC cases by ICD-9 and ICD-10. Confirmation of diagnosis using both biopsy (526) and pathology methods (638) was available for 99.49% of all cases. Only 7 cases were diagnosed using other methods including X-Ray. Of 1,171 CRC cases, colon cancer patients accounted for 65.67% and rectosigmoid junction and rectal cancer cases accounted for 34.33%. The mean age of the cases was 61.2 years old (SD: 9.4, range 20.0-74.0).

Table 4. Number and percentage of incident colorectal cancer cases aged 20-74 years old by the International Classification of Diseases 9th revision and 10th revision diagnosed in Newfoundland and Labrador in 1999-2003

CRC	ICD-9/ ICD-10	Sample (%)
Colon cancer		**769 (65.67)**
Malignant neoplasm of colon	153/ C18	769 (65.67)
Caecum	153.4/ C18.0	190 (16.23)
Appendix	153.5/ C18.1	1 (0.09)
Ascending colon	153.6/ C18.2	122 (10.42)
Hepatic flexure	153.0/ C18.3	31 (2.65)
Transverse colon	153.1/ C18.4	76 (6.49)
Splenic flexure	153.7/ C18.5	34 (2.90)
Descending colon	153.2/ C18.6	56 (4.78)
Sigmoid colon	153.3/ C18.7	230 (19.64)
Overlapping lesion of colon	153.8/ C18.8	4 (0.34)
Colon, unspecified	153.9/ C18.9	25 (2.13)
Rectum cancer		**402 (34.33)**
Malignant neoplasm of rectosigmoid junction	154.0/ C19	91 (7.77)
Malignant neoplasm of rectum	154.1/ C20	310 (26.47)
Malignant neoplasm of anus and anal canal	154/ C21	1 (0.09)
Anus, unspecified	154.3/ C21.0	1 (0.09)
CRC		**1,171 (100.00)**

Among 702 CRC cases in this study, 335 cases with intermediate or high familial risk and 367 with low familial risk were identified (14 cases with familial risk unidentified). The familial risk was identified by genetic counselors reviewing the familial history questionnaire returned by cases. The proband is classified as belonging to

either a high familial risk family, an intermediate familial risk family, or a low (sporadic) risk family (Box 1). This criteria has been used in the ON study of CRC [361].

There were a total of 68 MSI-H CRC cases and 634 MSI-L or MSS cases (45 cases with MSI unidentified). Tumour tissues were sought from hospital pathology laboratories and stored in the biospecimen repositories of the Faculty of Medicine at Memorial University of Newfoundland. MSI status was assessed from matched normal and tumour tissue from formalin fixed, paraffin-embedded blocks. MSI-H and MSI-L or MSS of all CRC cases were further identified through the analysis of blood samples obtained from cases according to the published international guidelines [120].

Box 1. Criteria used to classify probands in the Newfoundland Familial Colorectal Cancer Registry (NFCCR)

High familial risk/HNPCC (Amsterdam criteria1):

1. At least three relatives with colorectal cancer, one a first degree relative to other two, and
2. At least two successive generations affected with colorectal cancer, and
3. Colorectal cancer diagnosed under 50 year in at least one affected member, and
4. Does not have Familial Adenomatous Polyposis (FAP).

Intermediate familial/other risk (familial [#1-3], other (pathologic[#5-11], other [#4.12])):

1. Proband has two relatives with any of the HNPCC cancers[2] and 2 of the 3 are first degree relatives, or
2. any family member with an HNPCC cancers[2] ≤35 years of age, or
3. Proband <50 and relative with colon cancers <50 (1st or 2nd degree relative only), or
4. Proband ≤35 years of age, or
5. Proband with multiple primary colon cancers, or
6. Proband with other multiple primary colon cancer(s)[2], or
7. Proband has multiple polyps, or
8. Peutz-Jeghers or hamartomatous polyps, or
9. Juvenile polyp, or
10. Inflammatory bowel disease, or
11. Unusual colorectal cancer histologies[3], or
12. Ashkenazi Jewish

Low (sporadic) risk

1. All other colorectal cancer cases (probands) not classified as high or intermediate risk or high risk

Note: [1] [17]. [2] Colorectal, endometrial, gastric, small bowel, gastroesophageal, liver, pancreas, biliary tract, ovarian, kidney, ureter, brain, and lymphoma. [3] Carcinosarcoma, adenosquamous, spindle cell, metaplastic, choriocarcinoma, signet ring, undifferentiated, trophoblastic differentiation, small cell neuroendocrine carcinoma.

4.2.1.2. Recruitment of controls

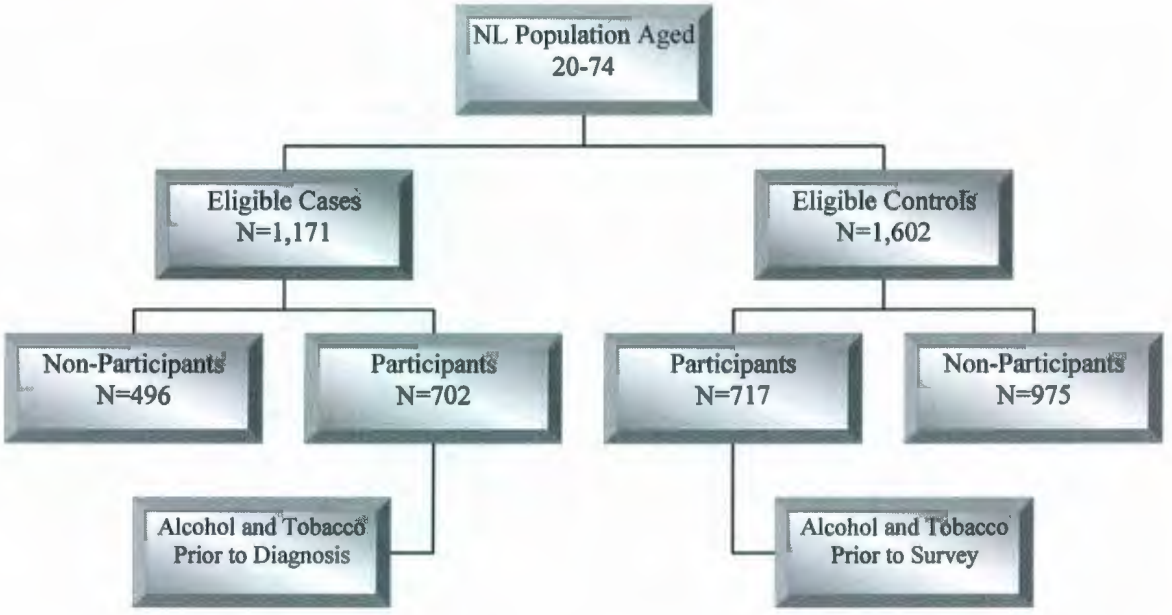
Eligible controls were NL residents between 20 and 74 years old, and without a diagnosis of previous CRC. Controls were frequency-matched with cases according to sex and five-year age group to improve the efficiency of the study. Controls were randomly selected from the NL population using the RDD method. Bell Aliant, one of North America's largest regional communications providers supplied 238 non-institutional exchanges (i.e., the three-digit prefix of a seven-digit telephone number), with working banks of four digit numbers used for residential customers. Non-active numbers, fax numbers, or non-residential numbers were removed from the residential telephone list. A list of 192,000 possible residential telephone numbers was provided by Bell Aliant based on the total residential lines in the working banks. This list was used to randomly select numbers for contact. Experienced interviewers made the initial contact by dialing the randomly selected telephone numbers in a sequential order until the desired number of controls was reached. A total of 15,500 random residential telephone numbers were randomly selected to be used for recruiting controls. The recruitment and survey of controls were carried out during the period between January 2004 and December 2006.

4.2.1.3. Participating rates

A total of 1,171 cases or 84.4% of eligible cases consented to participate in the study and were sent the study package. Of those cases, 702 or 59.9% completed and returned the questionnaires. Participating cases (702) accounted for 50.6% of all eligible cases (1,388). Among 1,602 eligible controls or 78.9% of eligible controls identified

using RDD who consented verbally to participate in the survey, a total of 717 controls which accounted for 44.8% of consented controls (1,602) or 35.3% of eligible controls (2,030) returned the survey packages and the signed consent forms at the end of December 2006. A detailed description of the recruitment of controls has been reported elsewhere [354].

Figure 2. Population-based case-control design of colorectal cancer in Newfoundland and Labrador



4.2.2. Data collection

All participants were asked to complete three self-administered questionnaires in the survey package; these questionnaires and data collection procedures have been utilized in the ON study of CRC [361]. The three questionnaires included in this survey package were as follows: (i) a Personal History Questionnaire (PHQ), (ii) a Family

History Questionnaire (FHQ), and (iii) a Food Frequency Questionnaire (FFQ). The tobacco smoking, alcohol consumption and other epidemiological risk factors were derived from the PHQ. The questionnaires were mailed to all consenting eligible participants with self addressed stamped envelopes. If a participant was unable to return finished 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. There were 258 cases who died during the study period, and 143 who died before the survey was conducted. Therefore, proxies of deceased cases were used to complete the survey. Variables of tobacco smoking, alcohol consumption and covariates used in the analyses of this thesis were derived from the PHQ in Appendix II.

4.2.2.1. Estimate of tobacco smoking

The reported or derived variables of smoking included in the analyses are summarized in Table 5. Tobacco smoking, including cigarettes, cigars and pipes, was investigated. Subjects were classified into the cigarette smoking group (smoker) if they had smoked one cigarette a day for three months or longer, and the non-cigarette smoking group (non-smoker) if they had not smoked one cigarette a day for three months or longer. Cigarette smokers were further classified into former and current cigarette smokers. Former cigarette smokers were those who stopped smoking cigarettes about one year before cancer diagnosis or survey, and current cigarette smokers were those who still smoked at least one cigarette a day during the year prior to diagnosis or recruitment.

Former and current cigarette smokers were classified into two groups according to initiation of smoking in reference to the question: "When did you first start smoking at least one cigarette a day?" (younger than 16 years old and 16 years or older); both were also classified into three groups according to the number of cigarettes per day in responding to the question: "During periods when you smoked regularly, how many cigarettes did you typically smoke in a day?" (1-19 cigarettes daily, 20-29 and 30+); and classified into three groups of total number of years of cigarette smoking in responding to the question: "How many years, in total, did you smoke at least one cigarette a day for three months or longer (if stopped and restarted at least once, count only the time when smoking)?" (1-19 years, 20-29 and 30+); the three groups of number of years since starting to smoke cigarettes was estimated based on the initiation age of smoking and age at diagnosis (1-25 years, 26-35 and 36+); as were three groups of cigarette pack years (1-19 pack years, 20-39 and 40+).

Pack year is a way to measure the amount a person has smoked over a long period of time [232]. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked [232]. For example, one pack year is equal to smoking 20 cigarettes per day for one year, or 40 cigarettes per day for half a year, and so on. Additionally, years of abstention from smoking cigarettes were also estimated and smokers were classified into four groups: zero year of abstention from smoking, 1-19, 20-29 and 30+.

Table 5. Reported or derived variables of tobacco smoking included in the analyses

Tobacco types	Variables	Categories
Cigarette	Cigarette use	0 = Non-smoker 1 = Smoker
	Cigarette use status	0 = Non-smoker 1 = Former smoker 2 = Current smoker
	Age of smoking initiation	0 = Non-smoker 1 = <16 2 = 16+
	Cigarette years	0 = 0 1 = 1-19 2 = 20-29 3 = 30+
	Years since start smoking	0 = 0 1 = 1-25 2 = 26-35 3 = 36+
	Cigarettes daily	0 =0 1 = 1-19 2 = 20-29 3 = 30+
	Cigarette pack years	0 = 0 1 = 1-19 2 = 20-39 3 = 40+
	Years of abstention	0 = 0 1 = 1-19 2 = 20-29 3 = 30+ 4 = Non-smoker
Cigar	Cigar use	0 = No 1 = Yes
Pipe	Pipe use	0 = No 1 = Yes
Total tobacco (cigarette, cigar, Pipe) 1 cigar = 4 cigarettes 1 pipe = 2.5 cigarettes	Tobacco use	0 = Non-smoker 1 = Smoker
	Tobacco use status	0 = Non-smoker 1 = Former smoker 2 = Current smoker
	Initiation age	0 = No 1 = <16 2 = 16+
	Smoking years	0 = 0 1 = 1-19 2 = 20-29 3 = 30+
	Cigarettes or equivalent daily	0 = 0 1 = 1-19 2 = 20-29 3 = 30+
	Smoking pack years	0 = 0 1 = 1-19 2 = 20-39 3 = 40+

The same questions were used to investigate cigar and pipe smoking monthly rather than daily. The number of cigar and pipe smoked were estimated and converted into equivalent cigarettes (one cigar = four cigarettes and one pipeful = two and half cigarettes) in total tobacco analysis [362,363]. Tobacco smokers were determined based on smoking one cigarette daily or one cigar/pipe monthly for three months or longer. Subjects were classified into the tobacco smoking group (smoker) if they had smoked one cigarette a day or one cigar/pipe a month for three months or longer, and non-tobacco smoking group (non-smoker) if they had not smoked. Tobacco smokers were further classified into former and current smokers. Former tobacco smokers were those who stopped smoking tobacco before cancer diagnosis or survey, and current tobacco smokers were those who still smoked at least one cigarette a day or cigar/pipe among during the year prior to diagnosis or recruitment.

4.2.2.2. Estimate of alcohol consumption

Reported or derived variables included in the analyses are presented in Table 6. There were four groups of alcoholic beverages investigated in the PHQ: (1) beer, hard cider (at least 3% alcohol); (2) wine; (3) sake, sherry, port; and (4) spirits, liquor mixed drinks, brandy, liqueurs. Questions were asked to determine the level of consumption of the four types of beverages: "In your 20s, did you ever consume any alcoholic beverages at least once a week for 6 months or longer?"; answers included "yes", "no" and "don't know". Respondents who answered yes were required to report "For how many years?", and then to answer "During those years, how much did you typically consume?", with

response option of the number of 12 ounce cans or bottles of beer, 4 ounce glasses of wine, 1 ounce serving of sake, or 1 ounce shots liquor or spirits per day, per week and don't know. The same questions were asked of respondents about their experiences in their 30s and 40s, and 50s. Two questions were asked to estimate the number of alcoholic beverages a week: "When you were in your 20s, how many years in total did you consume at least one alcoholic beverage (of any type) a week?", with answer of the years consumed; the second question was used to summarize the average alcohol consumption and the answer was the number of alcoholic beverages a week: "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." The same questions were asked concerning their experience in their 30s and 40s and 50s. Sake measures were merged into spirits measures because very few subjects reported drinking sake.

This thesis defined beer drinkers if they ever consumed beer once a week for 6 months or longer or beer non-drinkers; wine drinkers if they ever consumed wine once a week for 6 months or longer or wine non-drinkers; spirits drinkers if they ever consumed spirits once a week for 6 months or longer or spirits non-drinkers; Subjects were classified as alcohol drinkers if they ever consumed any alcoholic beverages once a week for 6 months or longer, or as alcohol non-drinkers. Derived variables on specific beverages were number of drinking years (0, 1-19, 20+), number of drinks daily/weekly (0, 1-2, 3+) and number of litres of absolute alcohol yearly (0, 1-4, 5+). Derived variables on total alcohol consumption in the analysis included types of beverage (0, 1-2 3+),

number of drinking years (0, 1-19, 20+), number of drinks daily (0, 1-2, 3+), and number of litres of absolute alcohol yearly (0, 1-4, 5-14, 15+).

Table 6. Reported or derived variables of alcohol consumption included in the analyses

Alcohol use	Variables	Categories
Beer	Beer drinker	0 = No
		1 = Yes
	Drinking years	0 = 0
		1 = 1-19
		2 = 20+
	Drinks daily	0 = 0
		2 = 1-2
		3 = 3+
	Litres yearly	0 = 0
		1 = 1-4
		2 = 5+
Wine	Wine drinker	0 = No
		1 = Yes
	Drinking years	0 = 0
		1 = 1-19
		2 = 20+
	Drinks weekly	0 = 0
		1 = 1-2
		2 = 3+
	Litres yearly	0 = 0
		1 = 1-4
		2 = 5+
Spirits	Spirits drinker	0 = No
		1 = Yes
	Drinking years	0 = 0
		1 = 1-19
		2 = 20+
	Drinks daily	0 = 0
		1 = 1-2
		2 = 3+
	Litres yearly	0 = 0
		1 = 1-4
		2 = 5+
Total alcohol	Drinker	0 = No
		1 = Yes
	Type of beverage	0 = No
		1 = One-two
		2 = Three+
	Drinking years	0 = 0
		1 = 1-19
		2 = 20-39
		3 = 40+
	Drinks daily	0 = 0
		1 = 1-2
		2 = 3-4
		3 = 5+
	Litres yearly	0 = 0
		1 = 1-4
		2 = 5-14
		3 = 15+

4.2.2.3. Covariates

The association of alcohol intake and tobacco smoking with the risk of developing CRC was investigated after adjusting for potential confounding of various demographic variables, chronic conditions and lifestyle measures. Specific covariates available for this thesis include age, sex, urban and rural residence, census division, place of birth, race, marital status, education attainment, household income, family CRC history, other cancer history, diabetes, cholesterol level, aspirin use, eating fruits, eating vegetables, eating red meats, body weight, and physical activity.

Respondents were classified into three age groups (20-54, 55-64 and 65+), two groups of birth place (those born in Canada or not), two racial groups (Caucasians or others), two education groups (high school completed or less, and higher than high school education), two groups of household income groups (less than $30,000 or no income, and $30,000 or more), two groups of marital status (currently married/living as married, and other marital status including single, never married, separated, divorced or widowed), and two groups of residential areas (urban and rural). An urban area has a minimum population concentration of 1,000 persons and a population density of at least 400 persons per square kilometre [218,364]. All territory outside urban areas is classified as rural. Technically, urban and rural residences were determined based on the definition of rural postal codes (i.e., individuals with a "0" as the second character in their postal code using Canada Postal System) [218]. There are 10 census divisions in NL [364]; using the postal

codes reported by the respondents, subjects were classified into 10 census divisions to examine geographical variation in incidence of CRC in NL, and adjust for spatial effect in the association.

Respondents were classified into two groups: those having a family history of CRC and those with no family history of CRC; those having other cancers diagnosed previously and those without previous cancer diagnosis; those having and not having been diagnosed with diabetes mellitus. Cholesterol level was investigated using response to the question: "Has a doctor ever told you that you had high cholesterol? If your doctor told you it was borderline, please tick 'no'."; answer choices included 'yes' and 'no'. Respondents were classified into those who did or did not regularly use aspirin (e.g. Anacin, Bufferin, Bayer, Excedrin, Ecotrin).

Eating fruits was investigated using response to the question: "About one year before your recent cancer diagnosis or investigation, on average, how often did you eat a piece or 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). Respondents were classified into two groups: <3 servings per day, 3+ servings per day. Eating vegetables was investigated using response to the question: "About one year before your recent cancer diagnosis or investigation, on average, how often did you eat a piece or serving of vegetables? Please include green salads, beans, lentils, etc., and potatoes (not packaged potato chips)." A serving of vegetables is: 1 cup raw; leafy vegetables; ½ cup of other vegetables, cooked or chopped raw; or 6 ounces of

vegetable juice. Respondents were classified into two groups: < 3 servings per day, 3+ servings per day.

Eating red meat was investigated using response to the question: "About one year before your recent cancer diagnosis or investigation, 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); and red meats include: beef, steak, hamburger, prime ribs, beef hot dogs, beef-based processed meat, veal, pork, bacon, pork sausage, ham, lamb, venison. Respondents were classified into two groups: <3 servings of red meats per day, 3+ servings per day.

Respondents were classified into non-obese (body mass index-BMI < 30) and obese (BMI $\geq$ 30). BMI was estimated based on the height and weight questions: "About how tall are you, without your shoes on?"; and "How much did you weigh about one year before your recent cancer diagnosis or investigation?" Respondents were classified into physically active and non-physically active groups. Physically active was defined as participating regularly in physical activity including walking, jogging, running, bicycling, swimming laps, playing tennis; playing squash or racquetball; doing calisthenics or aerobics; vigorous dancing, using a rowing machine and lifting weights; playing football, soccer, rugby or basketball; doing heavy household work (such as using a non-power mower), shoveling, moving heavy loads, scrubbing floors; and doing any other strenuous activities including skiing, skating, hockey, hunting, sledding, tobogganing or water-skiing for a total of at least 30 minutes a week – and respondents were asked about these kinds of physical activity in their 20s, 30s and 40s, and 50s.

4.3. Data analyses

4.3.1. Assessing non-participation bias of cases and controls

Non-participation bias was assessed based on the database of the NL population-based case-control study of CRC in which some demographic and clinical variables of eligible cases and some demographic variables of eligible controls were available [365,366]. Differences between the eligible population and the participant population are of great importance as they may influence both the internal and the external validity of the study [365]; therefore an examination of these differences is an important part of this thesis. To determine non-participation bias, this study compared the differences in demographic characteristics between participating and non-participating controls, and the differences in demographic and clinical characteristics between participating and non-participating cases. The study also compared the differences in age, gender, rural-urban area and census division between the eligible cases and controls, and between participating cases and controls (other epidemiological factors on participating cases ad controls have been collected and analyzed in Chapters 7 and 8). Chi-square technique was used to examine any differences in characteristics between participants and non-participants; and statistical analyses were completed using SAS 9.1 [367].

4.3.2. Assessing bias of self-reported tobacco smoking and alcohol intake

The validity of self-reported tobacco smoking and alcohol consumption was assessed in terms of coverage; that is, the extent to which tobacco smoking and alcohol consumption is determined based on survey responses accounts for all tobacco and alcohol sold [368,369]. This approach has been extensively applied in similar studies where more valid and reliable data cannot be obtained from respondents directly [370-372]. Per capita cigarettes smoked, and litres of absolute alcohol consumption yearly, were calculated based on the weighted sample of controls in the case-control study, and the results were compared to the provincial sale data and two national surveys.

4.3.2.1. Tobacco and alcohol consumption based on the case-control study data

Tobacco and alcohol consumption for the population 20-74 years of age was estimated based on the weighted sample of controls; a weighting variable was created because unequal controls by age and sex were selected to match with cases on age and sex. The relative weighting variable was created based on the proportion of age group and sex [373]. The estimate procedure of weighting can be seen in Table 7.

Table 7. The weighting estimate procedure

Age	Population Aged 20-74 in 2001 †				Controls Aged 20-74				Weighting	
	Population		Proportion		Control		Proportion			
	M (1)	F (2)	M (3)	F (4)	M (5)	F (6)	M (7)	F (8)	M (9)	F (10)
20-44	89,690	95,945	0.251	0.269	32	20	0.045	0.028	5.628	9.633
45-49	21,325	21,950	0.060	0.061	20	11	0.028	0.015	2.141	4.007
50-54	19,805	19,890	0.055	0.056	49	53	0.068	0.074	0.812	0.754
55-59	15,055	15,105	0.042	0.042	59	49	0.082	0.068	0.512	0.619
60-64	11,470	11,410	0.032	0.032	90	66	0.126	0.092	0.256	0.347
65-69	9,465	9,695	0.027	0.027	79	48	0.110	0.067	0.241	0.406
70-74	7,620	8,655	0.021	0.024	95	46	0.132	0.064	0.161	0.378

Note: † 2001 Census data from Statistics Canada. (1)-males aged 20-74 in 2001. (2)-females aged 20-74 in 2001. (3)-proportion of males by age. (4)-proportion of females by age. (5)-male controls. (6)-female controls. (7)-proportion of males by age. (8)-proportion of females by age. (9)-weighting for males by age=M(3)/M(7). (10)-weighting for females by age=F(4)/F(8).

First, annual per capita tobacco and alcohol consumption were estimated using the sample of controls in the case-control study [350,374]; the results were compared to the sales data of tobacco and alcohol in NL. Annual per capita tobacco consumption (PCTC) per smoker aged 20-74 years old was derived as follows:

$$\text{PCTC} = \frac{\text{Annual tobacco consumption in numbers for smokers}}{\text{Number of smokers in the sample of controls (20-74 years of age)}}$$

where annual tobacco consumption in numbers is equal to sum of (number of cigarettes smoked daily times 365 for each smoker) in the sample of controls. Per capita tobacco consumption was estimated for cigarettes and total cigarettes (cigarettes, one cigar = 4 cigarettes and one pipe = 2.5 cigarettes). Annual smoking packs of cigarettes and total cigarettes (one pack = 20 cigarettes) were also estimated based on the weighted sample of

controls in the case-control study; and the results were compared to the sales data of tobacco in NL to assess the accuracy of self-reported tobacco consumption. Cigarette smoker was defined as someone having smoked one cigarette a day for three months or longer and tobacco smoker was defined as having smoked one cigarette a day or one cigar/pipe a month for three months or longer.

Annual per capita alcohol consumption (PCAC) per drinker aged 20-74 years old was derived as follows:

$$\text{PCAC} = \frac{\text{Annual absolute alcohol consumption in litres for drinkers}}{\text{Number of drinkers in the sample of controls (20-74 years of age)}}$$

where annual absolute alcohol consumption in litres equals the sum of [drinking years times litres of alcohol consumed daily in 20s, 30s and 40s, and 50s (1 drink = 17.2 ml = 0.0172 litres in Canada [370]) times 365 for each drinker] in the control sample divided by sum of drinking year for drinkers in the control sample. Drinker was defined as "consuming any alcoholic beverages once a week for 6 months or longer" in the case-control study of CRC. PCAC was also estimated for the three major categories of alcoholic beverages (beers, wines and spirits). Percentage of annual alcohol consumption from beers, wines and spirits to total alcohol consumption was also estimated based on the weighted sample of controls in the case-control study. The results were compared to the sales data to assess the accuracy of self-reported beer, wine and spirit drinking.

Second, the per capita tobacco and alcohol consumption, and the percentage by subgroups, were estimated using the weighted sample of controls from the case-control

study. The results were compared to the estimates from the CCHS data to examine any discrepancies of tobacco and alcohol consumption in the case-control study and the CCHS.

Third, tobacco and alcohol consumption by subgroups among cases and controls in the case-control study of CRC was analyzed, as was the alcohol consumption by types of beverage. The aim of these analyses was to examine the patterns of tobacco and alcohol consumption among cases and controls, and thus find any differences in the self-reported tobacco and alcohol consumption between cases and controls.

The statistical analyses were performed using SAS 9.1 [367]. SAS PROC SURVEYMEANS was used to calculate the mean tobacco and alcohol consumption for types of beverage and subgroups; and SAS PROC TABULATE was used to calculate the percentages of tobacco and alcohol consumption for subgroups.

4.3.2.2. Tobacco and alcohol consumption based on the sales data

The tobacco smoked by smokers aged 20-74 was estimated based on the proportion of cigarettes consumed by smokers aged 20-74 years old to cigarettes smoked by daily and occasional smokers aged 12 years and older (0.9331 for NL) in CCHS 1.1. The annual litres of alcohol consumption for drinkers aged 20-74 years old were estimated using a proportion of alcohol consumption for population aged 20-74 to population aged 12 years and older (0.8956 in NL) in CCHS 1.1. The average annual per capita cigarette and alcohol consumption were estimated using the average annual cigarette and litres of alcohol sold for those aged 20-74 years old, dividing by the average

annual numbers of smokers or drinkers aged 20-74 years old from 1980 to 2003. The percentage of alcohol consumption from beer, wine and spirit to total alcohol consumption was estimated for the population aged 20-74 years old. The statistical analyses were performed using SAS 9.1 [367].

4.3.2.3. Tobacco and alcohol consumption based on the national survey data

The estimate of annual per capita litres of alcohol consumption per drinker among Canadians aged 20-74 in NL was based on CCHS 1.1 and CCHS 3.1. The last 7 days method was used to estimate alcohol consumption [371]. This method requires people to complete a retrospective 'diary' showing how much alcohol they drank on each of the last 7 days [371]. The overall volume of ethanol for the week is the sum over all days of the number of drinks times the litres of ethanol assumed to be in a standard drink [371]. In Canada, a standard drink equals to 0.0172 litres [370]. In the 2001 CCHS, the respondents were required to report the number of drinks of beer, wine, liquor or any other alcoholic beverage each day in one week prior to the interview day. The number of drinks in the past year was thus estimated by the number of drinks consumed in one week and multiplying this by 52 weeks.

Similarly, the number of cigarettes smoked yearly was estimated based on the number of cigarettes per day as reported multiplied by 365 days among daily smokers. The number of cigarettes smoked by occasional smokers who have smoked at least 100 cigarettes was estimated based on the questions: "On the days that you smoke, about how many cigarettes do you usually have?" and "In the past month, on how many days have

you smoked 1 or more cigarettes?" The CCHS survey weights were incorporated in the calculations to adjust for the sampling method. The rescaled weighting variable was used in the analyses [375]. The weight variables used by Statistics Canada were rebased to the sample sizes. This ensures that adjustments for sampling methods are retained, and the sample is maintained at the sample size rather than the population estimate. SAS PROC SURVEYMEANS [367] was performed to calculate per capita litres of alcohol and amount of tobacco use. SAS PROC TABULATE was used to calculate the percentages of alcohol consumption and cigarettes smoked by subgroups.

4.3.3. Effects of tobacco smoking and alcohol consumption on colorectal cancer

4.3.3.1. Descriptive analyses

The first step of data analysis was careful scrutiny of the raw data for error and correction of such errors, because the dataset involved various types of data saved in separate tables in Microsoft Access format. The data were reviewed for accuracy, consistency, completeness and manipulation. The variables were grouped in order to be compared with other studies. Chi-square analyses were performed to examine the distribution of each variable including exposure and covariates among cases and controls to see if it appeared reasonable and to help spot data errors [351]. The prevalence rate of lifetime alcohol use and tobacco smoking was estimated for subgroups such as male and female, and the 95% CI of the difference in the prevalence rate was calculated to test the null hypothesis that the prevalence rates (proportions) were identical [221].

4.3.3.2. Multivariate multilevel regression analyses

First, applying multivariate multilevel logistic regression techniques investigate any potential clustering of CRC in a geographical area [376]. The F-test examined significant differences in the incidence between each division and the province [376]; and the incidence rates were estimated using a multilevel model because incidence rates are subject to random variation and may be inaccurate, particularly in small areas [376]. This problem can be alleviated by obtaining shrunken incidence estimates using a random effect model with small areas taken as random [376]. The data were analyzed in binomial form with the dispersion parameter fixed at one. This prevents the area variance component from becoming incorporated into the dispersion parameter. The following SAS procedure was used to calculate the shrunken incidence estimate for each census division, and the shrunken incidence rates per 100,000 population are estimated using $[1+\exp[-(\text{int}\,ercept+\log it)]]^{-1}$:

```
PROC GLIMMIX;
CLASS cd;
MODEL crc/pop =  / LINK = LOGIT SOLUTION DDFM = KENWARDROGER;
RANDOM cd / SOLUTION;
RUN;
```

where cd = census division, crc = number of CRC incidence in census division, and pop = population in census division.

The prediction of five-year incidence rate was based on incident CRC cases for each division obtained from NCR for this study and the 2001 census population for each division. The number of cases for each division was adjusted in order to estimate total number of cases in each division. For example, new CRC cases aged 75 years and older in NL account for 25.5% of total CRC cases in 1999-2003 and total CRC cases for each division equal to cases aged 20-74 years old plus estimated cases aged 75 years and older [377]. The analyses showed that the incidence rate per 100,000 was significantly higher in census division (CD) No. 2, 8 and 9 than the provincial rate and the rate was significantly lower in CD No. 3 and 7 (see Table 8), suggesting a potential clustering effect on the association between CRC and alcohol and tobacco use. Therefore, the estimates of the ORs for drinking and smoking also involved adjustment for spatial effect.

Table 8. Observed and predicted five-year incidence rate (per 100,000) of colorectal cancer among Canadians aged 20-74 using multilevel model by Census Division in Newfoundland and Labrador in 1999-2003

CD □	Population	Cases Δ	Observed Rate	Predicted Rate	& 95% CI	Estimate	Probability
CD No. 1	242,875	799	32.88	31.07	21.81 - 44.23	0.1157	0.4794
CD No. 2	24,371	115	47.31	* 43.87	29.53 - 65.13	0.4621	0.0273
CD No. 3	19,370	25	13.11	* 13.98	8.41 - 23.24	-0.6844	0.0140
CD No. 4	22,162	67	30.07	28.38	18.52 - 43.47	0.0249	0.8982
CD No. 5	40,466	104	25.62	24.36	16.33 - 36.34	-0.1281	0.4883
CD No. 6	36,208	140	38.57	36.13	24.52 - 53.20	0.2671	0.1545
CD No. 7	37,335	51	13.60	** 13.71	8.80 - 21.34	-0.7043	0.0058
CD No. 8	42,188	203	48.14	* 44.99	30.92 - 65.42	0.4874	0.0168
CD No. 9	20,091	99	49.49	* 45.66	30.51 - 68.30	0.5023	0.0205
CD No. 10	30,279	61	20.26	19.67	12.78 - 30.25	-0.3427	0.1061
NL	515,345	1,664	32.29				

Note: □ CD: Census Division. CDs were delineated without reference to administrative or other forms of divisions in NL and are numbered [364]. CD No. 1=Avalon Peninsula-St. John's, CD No. 2=Burin Peninsula-Marystown, CD No. 3=South Coast-Channel-Port aux Basques, CD No. 4=St. George's-Stephenville, CD No. 5=Humber District-Corner Brook, CD No. 6=Central Newfoundland-Grand Falls-Windsor, CD No. 7=Bonavista/Trinity-Clarenville, CD No. 8=Notre Dame Bay-Lewisporte, CD No. 9=Northern Peninsula-St. Anthony, CD No. 10=Labrador-Happy Valley-Goose Bay. CD No. 11 (Nunatsiavut-Nain) was used for the fist time in the Canada 2006 Census; prior to 2006, Nunatsiavut-Nain was counted as part of CD No. 10. T-test *P<0.05 **P<0.01 ***P<0.001. Δ this analysis was based on all incidences of CRC 1999-2003 and eligible cases (1,388) accounted for 83.4%.

Second, Odds ratios (ORs) of CRC as estimates of relative risk, and the corresponding 95% confidence intervals (CIs), were computed separately according to various measures of cigarette smoking and alcohol drinking, and using multivariate multilevel logistic regression [376]. Each measure of smoking and drinking evaluated was modeled independently of one another given that these measures were highly correlated. Those who had never smoked served as the reference group in the analyses for smoking and those who had never drunk alcohol served as the reference group in the analyses for drinking. Age, sex and census division were included in all the analyses for smoking and drinking.

Other covariates for inclusion were based on a p-value of univariate test and correlation with other variables. Based on univariate logit analysis of the pooled data set, any variable whose univariate test had a p-value < 0.20 was considered as a candidate for the multivariate logistic regression analyses [219]. All selected covariates by univariate analysis were included in the models regardless of their "statistical significance". The rationale for this approach is to provide as much control of confounding as possible within the given data set [219]. This is based on the fact that it is possible for individual variables not to exhibit strong confounding, but when taken collectively, considerable confounding may be present in the data [219]. Independent variables with particularly high inter-correlations (> 0.30) were identified, less precise measures were excluded [220] and the variable pool was reduced to avoid synonymous variables and collinearity [221]. The

mean of the non-missing values for numeric variables was used as the estimate of missing numeric data, and the mode (most frequent) value is used as the estimate of missing categorical data [378]. Testing for linear trends was carried out by representing the categories of exposure with ordinal variables considered as continuous, and examining the significance of the coefficient with a z-test [351,379]. All statistical tests performed were two-sided. Stratification analyses were performed to examine any interaction effect by sex, drinking/smoking status, weight (BMI), survival status of cases, subsite of CRC, familial risk level and MSI status of cases.

The conventional logistic model ignores the hierarchical structure of the data and treats aggregate exposure as if it was measured at individual level. In this thesis, the dependent variable is incidence of CRC (case/control); the risk factor of interest is exposure to smoking/alcohol consumption; confounders included are age, sex and other covariates. The model is expressed by the following equation [219]:

$$Logit(\pi_{ij}) = \log\left[\frac{\pi_{ij}}{1-\pi_{ij}}\right] = \mu + \beta_0 ALCOHOL/TOBACCO_{ij} + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \cdots + \beta_n X_{nij}$$

where μ is the intercept parameter, and π_{ij} is the expected probability of incidence of CRC for the j^{th} individual in the i^{th} region (CDi) with smoking/alcohol consumption and other predictor variables ($X_1 \ldots X_n$). The SAS codes are shown below [367]:

PROC LOGISTIC DESC;
CLASS alcohol/tobacco covariates / PARAM = REF(Non-drinkers/Non-smokers) ORDINAL = INTERNAL;
MODEL crc = alcohol/tobacco covariates;
RUN;

The PROC LOGISTIC and MODEL statements are required [367]. The LOGISTIC procedure fits linear logistic regression models for binary or ordinal response data by the method of maximum likelihood. The maximum likelihood estimation is carried out with either the Fisher scoring algorithm or the Newton-Rephson algorithm. The DESC option reverses the default ordering of the response values so that crc = 1 (case) is modeled. ORDINAL = INTERNAL specifies the sorting order for the levels of the response variable. The CLASS statement names the classification variables to be used in the analysis. The PARAM = REF specifies the parameterization method for the classification variables.

The data can be modeled using multilevel logistic models on the same data with SAS GLIMMIX procedure [380]. In this approach, the influence of alcohol/tobacco exposure on the outcome (CRC incidence) is included through adjustment of random effect of geographical area (cd-census division) and other covariates. The model is expressed by the following equation [381]:

$$Logit(\pi_{ij}) = \log\left[\frac{\pi_{ij}}{1-\pi_{ij}}\right] = \mu + \beta_0 ALCOHOL/TOBACCO_{ij} + \gamma_j + \beta_1 X_{1j} + \beta_2 X_{2j} + \cdots + \beta_n X_{ij}$$

where μ is the intercept parameter, $\gamma_j \sim$ is a independently and identically-distributed random variable $(i.i.d.)$, $N(0,\sigma_g^2)$ and π_{ij} is the expected probability of incidence of CRC for j^{th} individual of the i^{th} category of smoking/alcohol consumption conditional on the predictor variables. The SAS codes are shown below [380]:

```
PROC GLIMMIX METHOD = RSPL;
CLASS cd tobacco/alcohol covariates;
MODEL crc(event=case) = tobacco/alcohol covariates;
/SOLUTION DIST = BINARY LINK = LOGIT DDFM = SATTETH ODDSRATIO;
RANDOM INTERCEPT / SUBJECT = cd SOLUTION;
NLOPTIONS TECH = NRRIDG;
RUN;
```

where DIST = BINARY and LINK = LOGIT are used to fit dichotomous data. Multinomial response (i.e., colon or rectum cancer, deceased case or living case, CRC cases with low or intermediate/high familial risk, and CRC cases with MSS/MSI-L or MSI-H) are modeled using DIST = MULTINOMIAL and LINK = CUMLOGIT.

The PROC GLIMMIX statement invokes the procedure [380]. The METHOD = RSPL specifies that the estimation technique in generalized linear mixed model is residual pseudo-likelihood with a subject-specific expansion. The CLASS statement instructs the procedure to treat the variables cd, as classification variable (i.e., it specifies that the linear predictor contains an intercept term that randomly varies at the level of the cd effect), and treat tobacco/alcohol and covariables as classification variables. The MODEL statement lists the same fixed effects as in the conventional approach, and the

event = case option instructs PROC GLIMMIX to model the probability of the incidence of CRC. The SOLUTION option in the model statement requests a listing of the solutions for the fixed-effects parameter estimates. The model option DDFM = SATTERTH uses the Satterthwaite method to adjust for denominator degree of freedom for tests of the fixed effects. The model option ODDSRATIO requests calculation of OR and the corresponding 95% CI. The RANDOM statement identifies the group structure in the mixed model. The random statement with "intercept" argument produces the random intercept model. The SUBJECT = cd statement fits a GEE-type model with independence working covariance structure and subjects (clusters) defined by the levels of cd. SAS has an alternative algorithm to ask for the random effect solutions by specifying the SOLUTION option in the RANDOM statement. Models fit with the GLIMMIX procedure usually require nonlinear optimization methods. One can control the optimization through options of the NLOPTIONS statement. In this study the TECH = NRRIDG option in the NLOPTIONS statement specifies an optimization technique of Newton-Raphson with ridging to help with the convergence of the procedure.

This design effectively controlled for intra-class correlations among census divisions within cells of the design (i.e. the tendency for observations adjacent within spatial units to be similar to each other). Measures from within one geographic area may be highly correlated, whereas those from different areas may be more likely to be independent of each other [381-384]. Given that groups of persons living in adjacent areas may share similar backgrounds and behaviors, and communicate with one another, loss of spatial independence between units may remain a problem. The multilevel analyses

conducted effectively dealt with the great bulk of spatial autocorrelation by virtue of nesting 10 census divisions.

Model fit was evaluated using the model chi-square [219,385,386]. The model chi-square is the difference between –2LL for the model with only a constant and –2LL for the model including all independent variables. If a model chi-square is statistically significant at the 0.05 level, this leads to rejecting the null hypothesis that all independent variables in the model are not related to the outcome. All statistical analyses were completed using SAS 9.1 [367]. SAS PROC MEANS, PROC FREQ, and PROC GLIMMIX procedures were performed to conduct these statistical analyses. The GLIMMIX procedure was used to model the data in the estimate of the OR for drinking and smoking to adjust for the random effect of geographic area as well as confounding effect of covariates [380]. All significance tests assumed two-tailed P values or 95% CIs.

Chapter 5 Assessing non-participation bias of cases and controls

5.1. Introduction

A trend of decreasing participation rates in population surveys is a growing concern in epidemiological research due to the increased likelihood of non-participation bias [313]. Low participation rates may compromise the generalizability of population survey data [314], especially when the percentage of non-participants is large, and when non-participants differ greatly from participants [387]. Non-participation is an important source of inaccurate reporting of alcohol and illicit drug use in population surveys [313,316], and the resulting underestimates of consumption may change the association between important variables and prevalence estimates [313].

Unfortunately, non-participation bias is usually difficult to determine because researchers rarely have information about non-participants. Few studies on non-participation bias in surveys in the alcohol and drug field have provided a clear answer to the issues raised. While some studies found no significant non-participation bias in estimating population attributes [317-319], others have indicated that bias exists [320]; and it has been suggested there is a serious chance of bias when a participation rate is below 70 percent [321]. The degree of non-participation bias is likely related to the focus of the study [320]. Several studies about direction of non- participation bias in surveys provide conflicting results. Some studies showed that non-participants were more likely to abstain from alcohol than participants [322,323], whereas others indicated non-participants who

drank were more likely to be heavier drinkers than participants [324]. In the population-based case-control study of CRC conducted in NL, of 1,171 eligible CRC cases who consented to participate in the CRC study, accounting for approximately 84.4% of the provincial eligible cases, 702 completed and returned the questionnaires, a participation rate of 59.9%. Of 1,602 controls meeting eligibility criteria and verbally consenting to participate in the study, accounting for 78.9% of eligible controls identified using RDD, 717 returned completed questionnaires and the participation rate was 44.7%. Therefore, non-participation is the main source of potential bias for assessing exposure to risk factors such as cigarette smoking and alcohol consumption for developing CRC. The aim of the study is to investigate the non-participation bias of cases and controls in this NL population-based case-control study.

5.2. Assessing methods and statistical analyses

Several demographic variables for eligible cases and controls and pathological characteristics for eligible cases were available from the existing database, and these variables are associated with many chronic conditions including cancer. Therefore, comparative studies on characteristics between participants and non-participants of cases and controls were conducted to assess non-participation bias [365,366]. Differences in the characteristics between the eligible population and the participant population are of great importance as they may influence both the internal and the external validity of the study [365]; therefore, an examination of these differences is an important part of study evaluation.

This study compared the differences in demographic characteristics between participating and non-participating controls, and the differences in demographic and clinical characteristics between participating and non-participating cases in order to determine non-participation bias. The study also compared the differences in age, gender, rural-urban area and census division between the eligible cases and controls, and between participating cases and controls (other epidemiological factors on participating cases ad controls have been collected and analyzed in Chapters 7 and 8). Chi-square technique was used to examine any differences in the characteristics between participants and non-participants of cases and controls. Statistical analyses were completed using SAS 9.1 [367]. SAS PROC FREQ was used to perform chi-square analyses.

5.3. Results

5.3.1. Eligible colorectal cancer cases and controls

When the study was carried out, 1,171 cases and 1,602 controls met the eligibility criteria and consented to participate in the study. The mean age of the cases and controls was 61.2 and 59.9 years old. Table 9 displays the frequency distribution of all eligible cases and controls by the variables known. While the chi-square analysis did not show any differences in the distribution of age and sex between eligible cases and controls, the analysis suggested more cases lived in rural area and more controls were selected from Census Divisions (CD) No. 4, 5, 6 and 7 compared to those eligible cases.

Table 9. The characteristics of eligible cases of colorectal cancer and controls in the case-control study

Characteristics	Eligible cases		Eligible controls	
	N	% Δ	N	% Δ
Age group (years)				
20-49	131	11.19	222	13.86
50-59	318	27.16	441	27.53
60-69	474	40.48	614	38.33
70-75	248	21.18	325	20.29
Sex				
Female	477	40.73	639	39.89
Male	676	59.27	963	60.11
Residence area				***
Urban	495	42.27	792	49.44
Rural	676	57.73	810	50.56
CD §				**
CD No. 1	562	47.99	743	46.38
CD No. 2	81	6.92	98	6.12
CD No. 3	18	1.54	21	1.31
CD No. 4	47	4.01	99	6.18
CD No. 5	73	6.27	155	9.68
CD No. 6	98	8.37	144	8.99
CD No. 7	36	3.07	54	3.37
CD No. 8	143	12.21	157	9.80
CD No. 9	70	5.98	72	4.49
CD No. 10	43	3.67	59	3.68
Total	1,171	100.00	1,602	100.00

Note: § CD: census division (see Table 8). Δ Column %. X^2: *P<0.05 **P<0.01 ***P<0.001.

5.3.2. Participating colorectal cancer cases and controls

While the chi-square analysis based on participating cases and controls was conducted, the study found no significant differences in age, sex and census division between the cases and the controls (Table 10). However, the analyses showed that more participating cases lived in rural area compared to those participating controls.

Table 10. The characteristics of participating cases of colorectal cancer and controls in the case-control study

Characteristics	Participating cases		Participating controls	
	N	% Δ	N	% Δ
Age group (years)				
20-49	88	12.68	83	13.86
50-59	211	30.06	209	27.53
60-69	274	38.89	282	38.33
70-75	129	18.38	143	19.94
Sex				
Female	273	38.89	293	40.86
Male	429	61.11	424	59.14
Residence area				*
Urban	302	43.02	355	49.51
Rural	400	56.98	362	50.49
CD §				
CD No. 1	329	46.87	327	45.61
CD No. 2	53	7.55	48	6.69
CD No. 3	9	1.28	8	1.12
CD No. 4	26	3.70	37	5.16
CD No. 5	43	6.13	78	10.88
CD No. 6	65	9.26	60	8.37
CD No. 7	27	3.85	28	3.91
CD No. 8	82	11.68	78	10.88
CD No. 9	43	6.13	30	4.18
CD No. 10	25	3.56	23	3.21
Total	702	100.00	717	100.00

Note: § CD: census division. Δ Column %. X^2: *P<0.05 **P<0.01 ***P<0.001.

5.3.3. Case participants and non-participants

Table 11 shows the participation rate of CRC cases and the frequency distribution of case participants and non-participants. The study did not find any significant relationship between participation and sex, urban-rural residence, census division, year of diagnosis, CRC site, and method of diagnosis. However, the analysis showed that younger people were more likely to respond to the request to participate in the survey;

and more deceased cases tended to be included in the study compared to those participants still living during the study period.

Table 11. Participation rate and the characteristics of study participants and non-participants of colorectal cancer cases in the case-control study

Characteristics	Rate & 95% CI √	Participant		Non-Participant	
		N	% Δ	N	% Δ
Age group (years)					**
20-49	67.18 (± 8.04)	88	12.54	43	9.17
50-59	66.35 (± 5.19)	211	30.06	107	22.81
60-69	57.81 (± 4.45)	274	39.03	200	42.64
70-74	52.02 (± 6.22)	129	18.38	119	25.37
Sex					
Female	57.23 (± 4.44)	273	38.89	204	43.50
Male	61.82 (± 3.61)	429	61.11	265	56.50
Residence area					
Urban	61.01 (± 4.30)	302	43.02	193	41.15
Rural	59.17 (± 3.71)	400	56.98	276	58.85
CD §					
CD No. 1	58.54 (± 4.07)	329	46.87	233	49.68
CD No. 2	65.43 (± 10.36)	53	7.55	28	5.97
CD No. 3	50.00 (± 23.10)	9	1.28	9	1.92
CD No. 4	55.32 (± 14.21)	26	3.70	21	4.48
CD No. 5	58.90 (± 11.29)	43	6.13	30	6.40
CD No. 6	66.33 (± 9.36)	65	9.26	33	7.04
CD No. 7	75.00 (± 14.15)	27	3.85	9	1.92
CD No. 8	57.34 (± 8.11)	82	11.68	61	13.01
CD No. 9	61.43 (± 11.40)	43	6.13	27	5.76
CD No. 10	58.14 (± 14.75)	25	3.56	18	3.84
Year of diagnosis					
1999	59.39 (± 6.36)	136	19.37	93	19.83
2000	66.17 (± 6.54)	133	18.95	68	14.50
2001	64.00 (± 5.95)	160	22.79	90	19.19
2002	57.46 (± 6.42)	131	18.66	97	20.68
2003	53.99 (± 6.02)	142	20.23	121	25.80
CRC site					
Colon	61.12 (± 3.45)	470	66.95	299	63.75
Rectum	57.71 (± 4.83)	232	33.05	170	36.25
Diagnosis method					
Biopsy	62.29 (± 4.15)	327	46.92	198	42.40
Pathology	57.90 (± 3.83)	370	53.08	269	57.60
Other (7 cases)					
Death					**
No	56.20 (± 3.46)	444	63.25	346	73.77
Yes	67.72 (± 4.69)	258	36.75	123	26.23
Total	59.95 (± 2.81)	702	100.00	469	100.00

Note: § CD: Census Division. √ Participation rate (%). Δ Column %. X^2: *P<0.05 **P<0.01 ***P<0.001.

5.3.4. Control participants and non-participants

Table 12 shows the participation rate of controls and the characteristics of control participants and non-participants. The chi-square analysis did not find any significant relationship between participation and age, sex, urban-rural residence or census division.

Table 12. The characteristics of control participants and non-participants in the case-control study

Characteristics	Rate & 95% CI √	Participant		Non-Participant	
		N	% Δ	N	% Δ
Age group (years)					
20-49	37.39 (± 6.36)	83	11.58	139	15.71
50-59	47.39 (± 4.66)	209	29.15	232	26.21
60-69	45.93 (± 3.94)	282	39.33	332	37.51
70-74	44.00 (± 5.40)	143	19.94	182	20.56
Sex					
Female	45.85 (± 3.86)	293	40.86	346	39.10
Male	44.03 (± 3.14)	424	59.14	539	60.90
Residence area					
Urban	43.83 (± 3.42)	355	49.51	455	51.41
Rural	45.71 (± 3.47)	362	50.49	430	48.59
CD §					
CD No. 1	44.01 (± 3.57)	327	45.61	416	47.01
CD No. 2	48.98 (± 9.90)	48	6.69	50	5.65
CD No. 3	38.10 (± 20.77)	8	1.12	13	1.47
CD No. 4	37.37 (± 9.53)	37	5.16	62	7.01
CD No. 5	50.32 (± 7.87)	78	10.88	77	8.70
CD No. 6	41.67 (± 8.05)	60	8.37	84	9.49
CD No. 7	51.85 (± 13.58)	26	3.91	26	2.94
CD No. 8	49.68 (± 7.82)	78	10.88	79	8.93
CD No. 9	41.67 (± 11.39)	30	4.18	42	4.75
CD No. 10	39.98 (± 12.50)	23	3.21	36	4.07
Total	44.76 (± 2.43)	717	100.00	885	100.00

Note: § CD: Census Division. √ Participation rate (%). Δ Column %. X^2: *P<0.05 **P<0.01 ***P<0.001.

5.4. Discussion

Participation bias arising from differences in characteristics between participants and non-participants is always a concern in epidemiological studies when participation

rates are low, as it may lead to biased estimates of prevalence and association [365]. Effects depend on selection criteria, defined by the investigator, and the extent of participation in a case-control study. Selection bias might affect the generalizability or the external validity of the results [365]. Differences in selection processes between the groups being compared may also affect the validity of the comparison (i.e. the internal validity of the study). The definitions of the different levels of population may also modify the hypothesis which is being tested in the study [365].

Cases in this study were obtained from the provincial population-based cancer registry (NCR). The study population was resident in NL, who had CRC diagnosed and reported to the registry between 1999 and 2003, and were aged 20-74 years old. A list of 1,171 NL residents aged 20-74 years old with a CRC diagnosis during the period from 1999 to 2003, who consented to participate in the study, was obtained through NCR to conduct the study of genetic and environmental factors of CRC. Cancer reporting is considered virtually complete in NL, since each Canadian province and territory has a legislated responsibility for cancer collection and control [388]. This is likely true, since these cases were obtained through the NCTRF which serves the whole province; almost all cases of CRC would come into hospital for diagnosis or treatment. Controls were randomly selected from the general population within the same age range using RDD [354].

In a case-control study, the cases should truly be cases and be newly incident with the outcome such as CRC; the cases should also be a total or representative series of cases from a defined eligible and source population [365]. The inclusion of some individuals who do not have the outcome in question within the case group will tend to

dilute the case group and bias the results of the study towards the null value. However, in this study, as described earlier, all the records of the NCR were reviewed in order to identify cases, pathology reports were sought to confirm the diagnosis, and pathological reviews for all cases were done. Over 99.9% of all 1,171 CRC cases were diagnosed for the first time between 1999 and 2003 using the methods of biopsy and pathology. Therefore all CRC cases identified can truly be considered eligible cases and would not dilute the final results.

Subjects in the control group were chosen to be true controls without the outcome of interest at the time the study was performed [365]; the control group was also chosen to be representative of the entire population at risk, and was matched to the cases in terms of five-year age group and sex. By comparing representative samples of CRC cases to controls who did not have the outcome, the study provided an estimate of the OR in underlying population. Misclassification, whereby some who were actually cases were included in the control group, would have a dilution effect and bias the results of the study towards the null value. It is possible that some controls developed a case after the survey. Where the estimated age-standardized incidence rate for CRC was 0.76‰ for males and 0.51‰ for females in NL in 2003 [388], the risk of this misclassification is likely to be too small to be important and this effect could not be considerable. Therefore, both case and control non-participation would be unlikely to bias the internal validity of research based on these participants; otherwise the research results tend to be more conservative.

The characteristics of eligible cases and controls who did not consented may differ from that of those who consented to participate in the study and potential biases may exist. While eligible cases and controls who consented to participate in the study accounted for 84.4% of eligible cases and 78.9% of eligible controls, the samples of cases and controls who consented to participate should be the representative of eligible respondents when a participation rate is over 70 percent [321]. However, low participation rates of eligible cases and controls may have affected the generalizability of the results.

Although the cases were identified in the provincial cancer registry and the controls were randomly selected from the provincial population, the generalizability of the results was still a concern because of low participation in this study. Since there is no information on tobacco smoking and alcohol consumption for non-participants, the study cannot evaluate any differences in exposure between participants and non-participants directly. A study on non-response bias in the use of alcohol and other drugs based on the 2004 Canadian Addiction Survey (CAS) showed non-response bias on some estimates of substance use, but the effects were small [389].

In this study, the analyses of control participation showed that there were no statistically significant differences in age, sex, and residence between participants and non-participants, suggesting no substantial selection bias. The analyses of cases did not show a significant difference in sex, year of diagnosis, residence of diagnosis, subsites of CRC (colon or rectum), or diagnosis method between participants and non-participants. The analyses found that more participant cases than non-participant cases were younger than 60 years old and in terminal stages at diagnosis, and this may bias the results.

However, the estimates of cigarette smoking and alcohol drinking in the national surveys (see Table 14 and 16 in Chapter 6) did not suggest more cigarettes smoked and alcohol consumed among younger than older Canadians. Furthermore, the estimates of the adjusted OR of living and deceased CRC cases for smoking and drinking in Chapter 7 and 8 (see Table 31 and 44) of this thesis did not demonstrate any substantial effects on the associations.

One concern was that more eligible cases lived in rural areas, and more cases who lived in rural areas tended to participate in the study. Several studies conducted in Canada found a significantly higher smoking prevalence in rural areas [390,391], and this may result in some degree of overestimation with respect to smoking among cases compared to controls. However, 59.2% of participating cases versus 57.0% participating controls living in rural areas is not too large and no substantial effect can be assumed. Another issue was that more controls were selected from census divisions 4, 5, 6 and 7 compared to cases. While the number of participating controls from these four census divisions accounted for a small proportion of total controls in the study, no substantial effect can be assumed.

In summary, while low participation rates among both cases and controls and significant differences in participation rates of cases between rural and urban residences, and different census divisions, non-participation bias cannot be excluded and therefore the results may not be generalized to the eligible population and other populations.

Chapter 6 Assessing reporting bias of self-reported tobacco smoking and alcohol intake

6.1. Introduction

The population-based case-control study of CRC conducted among NL residents to investigate the relationship between developing CRC, tobacco smoking and alcohol intake was based on self-reporting of participants. As described in depth in Chapter 4, cases and controls were asked about exposure in the past, and the validity of self-reported tobacco smoking and alcohol consumption was a concern because the accuracy of recall is usually related to the amount of time elapsed between the exposure and the recall [326]. Lifetime measures might be inaccurate because of the concern about the adequacy of long-term recall after 18 years [327]. For a variety of reasons, including issues of social desirability or sensitivity, subjects may not be willing to report an exposure accurately. When studies gather exposure data, subjects may underestimate the number of cigarettes they smoke and the amount of alcohol they drink [328].

Inaccurate report of exposure may produce bias away from the null [392-395] although, in general, inaccurate reporting biases the association toward the null value [396-399]. The validity of self-reported tobacco smoking and alcohol consumption may differ between cases and controls since the cases and controls by definition are people who differ with respect to their disease experience, and this difference may affect recall [325]. The bias caused by differential misclassification can either exaggerate the relative risk of

disease when cases overestimate and/or controls underestimate exposure or lessen an effect if cases underestimate and/or controls overestimate exposure [325]. Few studies have been conducted to investigate the accuracy of self-reported lifetime tobacco smoking and alcohol intake. Thus, the aim of this chapter is to examine the accuracy of self-reported lifetime tobacco smoking and alcohol consumption, and investigate the differences in the accuracy of self-reported tobacco smoking and alcohol consumption between cases and controls in the NL case-control study of CRC.

6.2. Assessment methods

Details on assessing methods and estimate procedures of self-reported tobacco smoking and alcohol consumption have been described in Chapter 4. This section briefly describes these assessment methods and analytical procedures.

6.2.1. Validity of self-reported tobacco and alcohol consumption

Annual per capita tobacco and alcohol consumption were estimated using the weighted sample of controls in the case-control study as controls were disproportionately selected from the general population to allow the study to match controls with cases on five-year and sex [374,400]. The results were compared to the sales data of tobacco and alcohol in NL. Per capita tobacco consumption was estimated for cigarettes and total cigarettes (cigarettes, one cigar = 4 cigarettes and one pipe = 2.5 cigarettes). Annual packs of cigarettes and total cigarettes were also estimated based on the weighted sample

of controls in the case-control study. The results were compared to the sales data of tobacco to assess the accuracy of self-reported tobacco consumption.

Per capita alcohol consumption was also estimated for the three major categories of alcoholic beverages (beers, wines and spirits). Percentage of annual alcohol consumption from beers, wines and spirits to total alcohol consumption was also estimated based on the weighted sample of controls in the case-control study. The results were compared to the sales data to assess the accuracy of self-reported beer, wine and spirit drinking.

Per capita tobacco and alcohol consumption and the percentage by subgroups were estimated using the weighted sample of controls from the case-control study. The results were compared to the estimates from the CCHS data to examine any difference in the patterns of tobacco and alcohol consumption between the case-control study and the national survey data. Tobacco and alcohol consumption by subgroups among cases and controls in the case-control study were estimated to examine the patterns of tobacco and alcohol consumption among cases and controls, and so found any differences in the validity of self-reported tobacco smoking and alcohol consumption between cases and controls.

6.2.2. Data analyses

Annual per capita tobacco and alcohol consumptions and percentages of tobacco and alcohol consumption were estimated using the weighted sample of controls in the case-control study, CCHS 1.1 and 3.1, the sales data of tobacco and alcohol. The results

were compared between these data sources to assess the accuracy of self-reported tobacco and alcohol consumption in the case-control study. The same analyses were also conducted among cases and controls to examine any differences in the reporting tobacco and alcohol consumption because of case status. The statistical analyses were performed using SAS 9.1 [367].

6.2.2.1. Analyses for the case-control study

Tobacco and alcohol consumption in the population aged 20-74 years old were estimated using the weighted sample of controls in the case-control study [350,374]. Average annual tobacco per smoker and alcohol consumption per drinker, and percentages of tobacco smoked by smokers and alcohol consumed by drinkers were also estimated for subgroups of the population. The results were compared to the sales data of tobacco and alcohol in NL. The analyses were also conducted between cases and controls in the case-control study.

6.2.2.2. Sales data analyses

The cigarettes and total cigarettes (cigarettes + cigars and pipe equivalent) smoked by smokers aged 20-74 was estimated based on the proportion of cigarettes consumed by those 20-74, using the proportion (0.9331) of cigarettes smoked by daily and occasional smokers aged 20-74 in CCHS 1.1. More information on CCHS 1.1 can be found elsewhere [357]. The annual litres of alcohol consumption for drinkers aged 20-74

were estimated using a proportion (0.8956) of alcohol consumption for population aged 20-74 to population aged 12 years and older in CCHS 1.1.

6.2.2.3. Analyses of the Canadian Community Health Surveys

The number of cigarettes smoked yearly was estimated based on the number of cigarettes per day as reported daily smokers multiplied by 365 days. The number of cigarettes smoked by occasional smokers was estimated based on the answer to the question: "On the days that you smoke, about how many cigarettes do you usually have?" and "In the past month, on how many days have you smoked one or more cigarettes?" The last seven days method was used to estimate alcohol use based on CCHS 1.1 and 3.1 [371]; a method that requires people to complete a retrospective 'diary' showing how much alcohol they drank on each of the last seven days [371]. The overall volume of ethanol for the week is the sum over all days of the number of drinks times the litres of ethanol assumed to be in a standard drink [371]. In Canada, a standard drink equals to 0.0172 litres [370]. The respondents were required to report the number of drinks of beer, wine, liquor or any other alcoholic beverage each day in one week prior to the interview day. The number of drinks in the past year was thus estimated by taking the number of drinks consumed in one week and multiplying this by 52 weeks. The rescaled weights were incorporated in the calculations to adjust for sampling method in the surveys [375].

6.3. Results

6.3.1. Accuracy of self-reported tobacco smoking and alcohol consumption

6.3.1.1. Estimate of tobacco smoking

Table 13 presents the estimates of tobacco smoked yearly based on the weighted sample of controls in the case-control study and the sales data. The estimated annual packs of cigarettes were 209 per smoker aged 20-74 years old in the NL case-control study which accounted for 71% of the estimate from the sales data (296). The estimates from the sales data in NL were not within 95% CI of the estimates from the case-control study, and the case-control study significantly underestimated tobacco smoking compared to the sales data.

Table 13. The estimates of per capita packs of cigarettes and total cigarettes yearly based on the weighted sample of controls in the case-control study compared to the sales data

Beverages	Average Annual Per Capita Cigarettes and Pack Years			
	N	Controls	95% CI (1935-2003) Γ	Sales Data (1980-2003) ψ
Cigarette packs	454	209	166 - 252	296
Total cigarette packs	454	214	170 - 257	

Note: Γ 2001 Canada census population aged 20-74 by age and sex to correct overrepresentation of males and older aged people in the weighted control sample in NL. ψ The sales data obtained from Health Canada, Wholesales sales data: cigarette and fine-cut sales charts 1980-2008 and cigarettes smoked by those aged 20-74 estimated based on proportion of cigarettes smoked for population 20-74 in CCHS 1.1 (2001), and population data obtained from Statistics Canada, downloaded from http://estat.statcan.gc.ca /cgi-win/CNSMCGI.EXE.

Table 14 presents the percentage and annual cigarette packs per smoker by subgroups in NL in CCHS 1.1 and 3.1, and in the weighted sample of controls in the

case-control study. The results showed that cigarette packs per smoker estimated from the case-control study for most of subgroups were similar to that from CCHS 1.1 and 3.1. The two CCHS datasets and the case-control study dataset showed similar patterns of cigarette smoking among Canadian smokers aged 20-74 years old. For example, those who had at least some post-secondary school education smoked 42.01% of cigarettes in CCHS 1.1, 50.94% in CCHS 3.1 and 50.48% in the case-control study, which represented the largest proportion of total cigarettes by education. However, the cigarette smoking was obviously underestimated by some groups such as females.

Table 14. Percentage and annual per capita cigarette packs per smoker by subgroups among Canadians aged 20-74 in Newfoundland and Labrador in the 2001 and 2005 Canadian Community Health Surveys and in the weighted sample of controls in the case-control study

Demographics	CCHS 1.1			CCHS 3.1			Sample of Controls		
	N Γ	% Ψ	Mean Ψ	N Γ	% Ψ	Mean Ψ	N Γ	% Ψ	Mean Ψ
Age									
20-49	729	75.98	262 (±15)	579	69.83	245 (±32)	46	60.82	211 (±72)
50-59	159	16.42	308 (±32)	156	20.56	293 (±38)	121	21.56	231 (±32)
60-69	72	5.71	257 (±43)	87	7.80	248 (±38)	192	13.60	207 (±26)
70-74	22	1.88	259 (±68)	31	1.82	218 (±80)	88	4.02	190 (±36)
Sex									
Male	480	59.23	308 (±19)	399	55.83	286 (±44)	300	70.48	284 (±65)
Female	502	40.77	226 (±15)	454	44.18	222 (±19)	147	29.52	134 (±38)
Marital status									
Married	634	68.18	280 (±15)	490	66.48	265 (±36)	362	81.92	208 (±50)
Wid/sep/div	143	9.49	270 (±31)	129	12.09	294 (±41)	72	10.35	193 (±59)
Single	205	22.33	239 (±28)	234	21.43	208 (±26)	13	7.73	398(±264)
School									
<high	352	39.11	314 (±23)	270	29.87	280 (±27)	163	31.68	292 (±43)
=High	165	18.88	290 (±26)	141	19.19	256 (±43)	78	17.84	221 (±73)
>high	465	42.01	230 (±17)	442	50.94	239 (±41)	206	50.48	181 (±37)
Total	982	100.00	269 (±13)	853	100.00	253 (±24)	447	100.00	214 (±44)

Note: Γ: unweighted CCHS 1.1-2001 survey, CCHS 3.1-2005 survey and control sample. Ψ: weighted estimates.

6.3.1.2. Estimate of alcohol consumption

Table 15 presents the percentage of each beverage consumed yearly and average annual litres of alcohol of beverages per drinker estimated in the weighted sample of controls in the case-control study and based on the alcohol sale data. Per capita litres of total alcohol consumption estimated in the case-control study were close to the estimates of the sales data. Each drinker consumed 13.20 litres of ethanol yearly (95% CI: 10.47 - 15.93) based on the case-control study data. The estimates of average annual litres of alcohol consumption per drinker (11.35) from the sales data were within 95% CI of the estimate from the weighted sample of controls.

Table 15. Percentage of each beverage consumed yearly and average annual per capita litres of ethanol per drinker estimated in the weighted sample of controls in the case-control study and based on the alcohol sales data

Beverages	Alcohol Consumption in Litres Per Drinker				Percentage of Each Beverage % †	
	Sales Data ‡ (1992-2003)	Control Sample (95% CI) (1940-2003)			Sales Data ‡ (1992-2003)	Control Sample (1940-2003)
Beer	6.52	N=453	6.84	5.17 - 8.50	57.42	51.80
Wine	0.70	N=453	1.45	0.87 - 2.04	6.16	11.04
Spirit	4.13	N=453	4.91	3.56 - 6.24	36.42	37.16
Total alcohol	11.35	N=453	13.20	10.47 - 15.93	100.00	100.00

Note: † litres for each beverage to total alcohol consumption on average yearly. ‡ The sales data of alcohol obtained from Statistics Canada, downloaded from http://estat.statcan.gc.ca/cgi-win/CNSMCGI.EXE and alcohol consumed by those aged 20-74 estimated based on proportion of alcohol consumption for population aged 20-74 in CCHS 1.1 (2001), and population data obtained from Statistics Canada, downloaded from http://estat.statcan.gc.ca/cgi-win/CNSMCGI.EXE.

Beer consumption accounted for 51.80% of total alcohol consumption, and wine and spirit consumption accounted for 11.04% and 37.16% respectively, based on the weighted sample of controls. Beer consumption tended to be underestimated and wine and spirit consumption tended to be overestimated based on the case-control study data compared to the sales data. The estimates of per capita alcohol consumption from beers and spirits from the sales data were within 95% CI of the estimates in the case-control study, but alcohol consumption for wines was significantly overestimated in the case-control study compared to the sales data.

Table 16 presents the percentage and annual per capita alcohol consumption by subgroups among Canadians aged 20-74 in NL in CCHS 1.1 and 3.1, and in the weighted sample of controls in the case-control study. The results show that per capita alcohol consumption was significantly underestimated in CCHS 1.1 and 3.1 for almost all subgroups. However, the drinking patterns generally remained unchanged in three samples. For example, the ratio of per capita litres of alcohol consumption for males versus females was 2.5 in the control sample, 1.9 in CCHS 3.1 and 2.4 in CCHS 1.1. The percentages of alcohol consumption within the subgroups varied in three samples in NL, but they showed similar patterns. For example, men consumed 77.75% of total litres of alcohol and women consumed 22.25% in the case-control study of CRC compared to 74.20% and 25.80% in CCHS 1.1, and 71.49% and 28.51% in CCHS 3.1.

Table 16. Percentage and annual per capita litres of absolute alcohol consumption per drinker by subgroups among Canadians aged 20-74 in Newfoundland and Labrador in the 2001 and 2005 Canadian Community Health Surveys and in the weighted sample of controls in the case-control study

Demographics	CCHS 1.1			CCHS 3.1			Sample of Controls		
	N Γ	% Ψ	Mean Ψ	N Γ	% Ψ	Mean Ψ	N Γ	% Ψ	Mean Ψ
Age									
20-49	1,180	71.12	6.60(±0.41)	1238	69.54	6.79 (±0.44)	65	66.57	12.60 (±3.80)
50-59	361	19.94	6.62(±0.87)	410	19.98	6.68 (±1.25)	140	21.12	15.43 (±4.37)
60-69	150	6.93	6.20(±1.81)	240	8.16	5.47 (±0.57)	174	9.78	13.58 (±2.79)
70-74	47	2.01	5.42(±1.63)	95	2.31	4.82 (±0.94)	74	2.53	12.55 (±3.48)
Sex									
Male	996	74.20	8.16(±0.55)	1,071	71.49	8.08 (±0.62)	339	77.75	17.88 (±4.06)
Female	742	25.80	4.18(±0.29)	912	28.51	4.49 (±0.32)	114	22.25	6.89 (±2.60)
Marital status									
Married	1,207	65.03	5.98(±0.36)	1,331	66.34	6.02 (±0.35)	384	83.27	12.75 (±3.01)
Wid/sep/div	206	7.87	6.85(±1.61)	234	9.01	8.16 (±3.06)	56	10.35	14.15 (±4.04)
Single	325	27.11	8.36(±1.03)	418	24.65	8.02 (±0.93)	13	6.39	20.34(±19.07)
School									
<high	423	20.84	6.59(±0.64)	381	17.00	7.00 (±0.97)	128	18.38	17.46 (±2.42)
=High	272	17.99	6.88(±0.92)	294	17.32	7.29 (±1.56)	73	12.35	13.85 (±5.30)
>high	1,043	61.17	6.44(±0.48)	1,308	65.68	6.32 (±0.39)	252	69.27	12.30 (±3.36)
Total	1,738	100.00	6.55(±0.36)	1,983	100.00	6.58 (±0.39)	453	100.0	13.20 (±2.73)

Note: Γ: unweighted CCHS 1.1-2001 survey, CCHS 3.1-2005 survey and control sample. Ψ: weighted estimates.

6.3.2. Tobacco smoking and alcohol intake and case-control status

6.3.2.1. Tobacco smoking and case-control status

Table 17 presents annual numbers and packs of cigarettes and total cigarettes (cigarettes, cigars and pipes) per smoker for cases and controls in the case-control study. While the control smokers smoked 218 packs of cigarette, and cigars and pipes equivalent to six packs of cigarettes on average per year prior to the survey, case smokers smoked 262 packs of cigarette, and cigars and pipes equivalent to four packs of cigarettes on average per year prior to their diagnosis of CRC. Cases smoked 40 more cigarette packs or total cigarette packs yearly than did controls (95% CI_{diff}: 42-45 and 41-44).

Table 17. Annual number and packs of cigarettes and total cigarettes for cases ad controls in the case-control study

Tobacco smoking	Case			Control		
	N	Mean	95% CI	N	Mean	95% CI
Cigarettes	504	5230	4859 - 5601	454	4352	4000 - 4705
Total cigarettes ∞	504	5325	4950 - 5701	454	4473	4115 - 4830
Cigarette packs	504	262	243 - 280	454	218	200 - 235
Total packs ∞	504	266	248 - 285	454	224	206 - 242

Note: ∞ 1 cigar = 4 cigarettes and 1 pipe = 2.5 cigarettes.

Table 18 presents the average annual cigarette packs per smoker by subgroups in the case and control samples in the case-control study. The results show similar patterns of cigarette smoking reported by smokers in both the case and control samples in NL. For example, cigarettes smoked by age groups of cases and controls accounted for 11.53% and 11.07% for aged 20-49, 29.30% and 28.54% for aged 50-59, 40.86% and 42.56% for aged 60-69, and 18.31% and 17.83% for aged 70-74.

Table 18. Average annual per capita cigarette packs per case and control smoker by subgroups in the case-control study

Demographics	Case				Control			
	N	%	Mean	95% CI	N	%	Mean	95% CI
Age								
20-49	62	11.52	245	196 - 294	46	11.07	238	168 - 308
50-59	152	29.29	254	223 - 285	121	28.55	233	199 - 267
60-69	196	40.86	275	241 - 308	192	42.55	219	191 - 247
70-74	91	18.32	265	224 - 307	88	17.83	200	166 - 234
Sex								
Male	345	75.34	288	263 - 313	300	76.13	251	227 - 274
Female	156	24.66	208	188 - 229	147	23.87	160	139 - 182
Marital status								
Married	400	79.00	260	240 - 281	362	77.66	212	194 - 229
Wid/sep/div	78	16.24	274	220 - 329	72	15.77	217	179 - 255
Single	23	4.77	273	189 - 357	13	6.56	499	199 - 798
Education								
<high school	242	50.45	275	247 - 303	163	39.43	239	205 - 274
=High school	80	16.19	267	212 - 322	78	17.09	216	180 - 252
>high school	179	33.36	246	219 - 272	206	43.48	208	185 - 232
Total	501	100.00	263	244 - 282	447	100.00	221	203 - 239

6.3.2.2. Alcohol consumption and case-control status

Table 19 presents the percentages of alcohol consumption (ethanol in litres) from each beverage to total alcohol consumption and per capita litres of alcohol from beverages consumed for cases and controls estimated in the case-control study. Case drinkers tended to consume more beer and fewer wines and spirits than control drinkers in NL. Case drinkers on average consumed 16.94 litres of ethanol per year prior to the CRC diagnosis, and controls consumed 14.34 - a significant difference between cases and controls (95% CI_{diff}: 2.45-2.69). While case drinkers consumed more beer (95% CI_{diff}: 2.21-2.36) and spirits (95% CI_{diff}: 0.26-0.41) than control drinkers did, control drinkers consumed more wine than case drinkers did (95% CI_{diff}: 0.03-0.06).

Table 19. Per capita litres of ethanol of beverages per case drinker and control drinker estimated in the case-control study

Beverages	Case				Control			
	N	% †	Mean	95% CI	N	% †	Mean	95% CI
Beer	432	56.38	9.55	8.33 - 10.77	453	50.60	7.27	6.27 - 8.28
Wine	432	5.63	0.95	0.73 - 1.17	453	6.94	1.00	0.79 - 1.21
Liquor	432	37.99	6.44	5.43 - 7.43	453	42.45	6.10	4.89 - 7.32
Total alcohol	432	100.00	16.94	15.12 - 18.76	453	100.00	14.37	12.53 - 16.22

Note: † litres for each beverage to total alcohol consumption.

Table 20 presents average annual litres of absolute alcohol consumption and percentage of alcohol consumption by subgroups in the case and control samples in NL. Case drinkers consumed more alcohol than control drinkers did for almost all subgroups

in NL. The percentages of alcohol consumption by subgroups show similar patterns of drinking reported by the drinkers in the case and control samples in NL. For example, male case drinkers consumed 90.41% of total alcohol consumed by case drinkers, and male control drinkers consumed 91.28% of total alcohol consumed by control drinkers.

Table 20. Annual l litres of absolute alcohol consumption per case and control drinker and percentage of alcohol consumption by subgroups in the case-control samples in the case-control study

Demographics	Case				Control			
	N	% †	Litres	95% CI	N	% †	Litres	95% CI
Age								
20-49	63	16.74	19.44	13.16 - 25.73	66	13.13	12.95	9.28 - 16.62
50-59	137	32.13	17.16	13.83 - 20.49	143	32.44	14.77	10.90 - 16.63
60-69	161	36.02	16.37	13.43 - 19.11	174	38.48	14.40	11.39 - 17.41
70-74	72	15.11	15.36	12.09 - 18.62	75	15.95	13.84	10.19 - 17.50
Sex								
Male	335	90.41	19.75	17.60 - 21.91	341	91.28	17.43	15.09 - 19.76
Female	97	9.59	7.24	4.89 - 9.57	117	8.72	4.85	3.81 - 5.89
Marital status								
Married	349	76.13	15.96	14.00 - 17.85	384	80.16	13.67	11.82 - 15.52
Wid/sep/div	62	18.32	21.62	15.95 - 27.29	56	15.84	17.86	10.16 - 25.56
Single	21	5.55	19.36	6.50 - 32.21	13	4.00	20.02	9.89 - 30.15
Education								
<high school	188	42.05	16.37	13.87 - 18.87	128	36.27	18.45	14.78 - 22.13
=High school	63	16.63	19.31	13.92 - 24.70	73	14.70	13.12	9.56 - 16.66
>high school	181	41.32	16.71	13.74 - 19.68	252	49.03	12.67	10.14 - 15.20
Total	432	100.00	16.94	15.13 - 18.76	453	100.00	14.37	12.53 - 16.22

Note: † litres for each subgroup to the sample.

6.4. Discussion

In the NL population-based case-control study of CRC, data on tobacco smoking and alcohol consumption were collected by means of self-administered questionnaires and thus potentially susceptible to reporting bias [365,401]. A general problem in measuring

tobacco smoking and alcohol intake, particularly over a lifetime, is the absence of a "gold standard" such as direct observation of smoking and drinking behaviours [371]. Self-reports are the simplest method of gathering the data but are prone to reporting bias since accuracy of recall is affected by the elapsed time since the event occurred, as well as the saliency of the event and its frequency of occurrence. Extending the reference period to a lifetime probably will affect the accuracy of such self-reports [402]. In the case-control study, the main protection against bias was the standardization of methods, so the questions were identical and presented in an identical fashion to both cases and controls. However, cases might have acknowledged smoking and drinking as a cause of CRC, and so more likely to remember more about tobacco smoking and alcohol consumption than controls, thus resulting in the overestimation of these exposures which can exaggerate the association [365].

In this thesis, the accuracy of self-reporting lifetime tobacco smoking and alcohol intake measures was estimated by a comparison of self-report versus sales statistics versus survey reports of tobacco smoking and alcohol consumption. The accuracy of self-reported lifetime alcohol consumption and tobacco smoke was assessed by a comparison with two external sources: alcohol and tobacco sales statistics, and self-reported alcohol consumption and tobacco use from CCHS. The study also compared the differences in the accuracy of self-reported alcohol and tobacco use between cases and controls to assess the differential misclassification bias because of case-control status.

The estimated annual numbers and packs of cigarettes and total cigarettes (including cigars and pipes) smoked were lower in the case-control study than the sales

data in NL. If including illegal tobacco products, the estimates of tobacco smoking from the case-control study might be greatly lower than actual tobacco smoking - about 22 percent of cigarettes smoked in Canada are illegal every year [403]. Per capita tobacco consumption in the case-control study tended to be underestimated compared to the national surveys. The results in this thesis are consistent with another study based on the NL case-control study which also shows an underestimate of cigarette smoking [354]. Although the estimates of tobacco smoking based on the two CCHS datasets and the case-control study dataset varied by subgroups, the estimates did not show any systematic changes. The results showed that the cigarette smoking appeared to obviously differ in some groups in three samples, but the three samples showed similar patterns of cigarette smoking. The results tended to show no systematic changes in the reporting of tobacco smoking in the case-control study of CRC and thus no substantial bias on the association can be assumed. These analyses also did not provide any evidence of inaccurate and differential report of tobacco smoking for cases and controls which might bias the association of CRC with drinking and smoking substantially.

The results of this thesis show a more accurate estimate of alcohol consumption in the case-control study than the cross-sectional surveys. Cross-sectional studies found alcohol coverage rates ranging from 40-60% in general populations [330]. The underestimates may reflect a general memory failure that afflicts all self-report methods [404]. Different questions on lifetime alcohol consumption designed in the NL case-control study may be the reason that the case-control study produced more valid estimates of alcohol consumption. In this study, the self-reported lifetime alcohol consumption in the

weighted sample of controls was relatively accurate compared to the sales data and two national surveys. Annual alcohol consumption of 13.20 litres per drinker, estimated based on the weighted sample of controls was higher than the estimates of 11.35 litres of alcohol from the alcohol sale data in NL, but estimate from the sales data was within 95% CI of the estimate from the case-control study data. This may be because the self-reporting of alcohol intake may include alcohol consumption from all sources including the retail sales, U-brew and U-vint production, home brewing, cross-border shopping and illegal channels; and the sale estimates were based on only the retail sales data [346]. The consumption of absolute alcohol from those unrecorded sources is now estimated to be about 19.5% in ON [405]. If the unrecorded alcohol consumption in NL is the same as that reported in ON, the estimate of alcohol consumption from the case-control study is relatively valid. In this study, beer consumption tended to be underestimated, and wine and spirits consumption tended to be overestimated in the case-control study compared to the sales data. Previous studies have shown that coverage rates of alcohol sales also varied by type of beverage although the rates were not totally consistent [316]. Several studies found that wine and spirits consumption can be more accurately estimated than beer because wine and distilled liquors drinkers may have more stable drinking patterns which can be more easily recalled [372,406,407].

Although the case-control sample produced a relatively higher wine and spirits and lower beer estimates compared to the sales data, the patterns of three types of beverage consumption remained unchanged. These patterns are the same as that in other cross-sectional surveys (i.e., the surveys generally produce relatively higher estimates of

wines and relatively lower estimates of beers) [370,371,408]. While only the wine consumption was significantly overestimated in the case-control study compared to the sales data and it accounted for a small proportion of total alcohol consumption, the overestimation of wine consumption did not produce a substantial effect on the estimate of total alcohol consumption and the association studied in this thesis. Therefore, alcohol consumption reports in the case-control study of CRC were valid.

The analyses on tobacco smoking and alcohol consumption by subgroups among cases and controls did not suggest any substantial differences in the reporting of tobacco smoking and alcohol consumption between cases and controls in the case-control study of CRC. Therefore, it was unlikely that inaccurate reporting of tobacco smoking and alcohol consumption have greatly biased the association. It was assumed that the misclassification of cigarette smoking is non-differential, which means that sensitivity and specificity of self-reported smoking was the same for cases and controls. Now suppose that self-reported smoking resulted in a smoking estimate that had 100% specificity but only 85% sensitivity. In other words, all the truly non-smokers were correctly classified as non-smokers, but there was an 85% chance that a smoker will be correctly classified as smoker and thus a 15% (95% CI: 13-17%) chance a smoker will be incorrectly classified as non-smoker. Under this circumstance, the relative risk of CRC due to smoking was underestimated (from 1.90 to 1.51). Similarly, as shown in Table 21, when all the truly smokers were correctly classified as smokers and 85% of non-smokers were correctly classified as non-smokers, a 15% (95% CI: 13-17%) chance that a non-smoker will be incorrectly classified as smoker. In such circumstances, the relative risk of

CRC due to smoking was also underestimated (from 1.57 to 1.51). Underestimated effects of misclassification for cigarettes daily can be also found.

Table 21. Effect of non-differential misclassification of cigarette smoking on colorectal cancer risk

	Smoking measure	Case	Controls	OR & 95% CI
NL CRC data †	Non-smoker	201	270	1.00
	Smoker	501	447	1.51 1.20-1.88
	Cigarettes daily			
	01-19	234	216	1.46 1.12-1.89
	20-29	193	175	1.48 1.13-1.95
	30+	74	56	1.78 1.20-2.63
Sensitivity = 0.95	Non-smoker	175	246	1.00
Specificity = 1.00	Smoker	527	471	1.58 1.26-1.99
	Cigarettes daily			
	01-19	246	227	1.53 1.10-1.99
	20-29	203	184	1.56 1.18-2.06
	30+	78	59	1.87 1.26-2.75
Sensitivity = 0.85	Non-smoker	113	191	1.00
Specificity = 1.00	Smoker	589	526	1.90 1.47-2.47
	Cigarettes daily			
	01-19	275	254	1.84 1.38-2.45
	20-29	227	206	1.87 1.39-2.53
	30+	87	66	2.24 1.51-3.33
Sensitivity = 1.00	Non-smoker	212	284	1.00
Specificity = 0.95	Smoker	490	433	1.52 1.22-1.90
	Cigarettes daily			
	01-19	223	202	1.49 1.15-1.93
	20-29	181	164	1.48 1.13-1.96
	30+	86	67	1.72 1.19-2.48
Sensitivity = 1.00	Non-smoker	236	318	1.00
Specificity = 0.85	Smoker	466	399	1.57 1.26-1.94
	Cigarettes daily			
	01-19	199	168	1.58 1.21-2.07
	20-29	152	137	1.49 1.12-1.98
	30+	115	94	1.65 1.19-2.27

Note: † assuming that there was s misclassification of cigarette smoking in the NL data.

When assuming that the misclassification of cigarette smoking is differential, which means that sensitivity and specificity of self-reported smoking was not the same for cases and controls. Table 22 presents the effect of misclassification of cigarette smoking on CRC risk. If more case smokers were incorrectly classified as non-smokers or more control non-smokers were incorrectly classified as smokers, the relative risk of CRC due to smoking will be underestimated slightly (see Panels C and D). Underestimated effects of misclassification for cigarettes daily can be also found.

When more control smokers were incorrectly classified as non-smokers, or more case non-smokers were incorrectly classified as smokers, the relative risk will be exaggerated or even reverse the relationship and make the results misleading. As shown in Panel A and B in Table 22, a statistically significant relationship appeared because 7% (95% CI: 5-9%) of control smokers were incorrectly classified as non-smokers or 13% (95% CI: 11-16%) of case non-smokers were incorrectly classified as smokers. When 19% (95% CI: 16-22%) of control smokers were incorrectly classified as non-smokers or 33% (95% CI: 30-37%) of case smokers were incorrectly classified as non-smokers, the relationship will be reversed. The same effect of misclassification for cigarette daily can also be observed. However, the comparative analyses in this chapter show that it was unlikely that any misclassification of smoking for cases and controls appeared.

Table 22. Effect of differential misclassification of cigarette smoking on colorectal cancer risk

Cigarettes	Sensitivity/ Specificity	Case/ Control	OR & 95% CI	Sensitivity/ Specificity	Case/ Control	OR & 95% CI
Non-smoker	NL data †	201/270	1.00	NL data †	201/270	1.00
Smoker		501/447	1.51 1.20-1.88		501/447	1.51 1.20-1.88
Cigs daily						
01-19		234/216	1.46 1.12-1.89		234/216	1.46 1.12-1.89
20-29		193/175	1.48 1.13-1.95		193/175	1.48 1.13-1.95
30+		74/56	1.78 1.20-2.63		74/56	1.78 1.20-2.63
	Panel A Control			Panel C Case		
Non-smoker	Sens = 0.94	201/241	1.00	Sens = 0.95	175/270	1.00
Smoker	Spec = 1.00	501/476	1.27 1.01-1.59	Spec = 1.00	527/447	1.82 1.45-2.29
Cigs daily						
01-19		234/230	1.22 0.94-1.59		246/216	1.76 1.35-2.30
20-29		193/186	1.25 0.95-1.64		203/175	1.79 1.36-2.37
30+		74/60	1.49 1.01-2.20		78/56	2.15 1.45-3.18
Non-smoker	Sens = 0.93	201/236	1.00	Sens = 0.90	145/270	1.00
Smoker	Spec = 1.00	501/481	1.23 0.98-1.54	Spec = 1.00	557/447	2.31 1.83-2.93
Cigs daily						
01-19		234/232	1.18 0.91-1.54		260/216	2.24 1.71-2.93
20-29		193/188	1.21 0.92-1.59		214/175	2.28 1.71-3.02
30+		74/60	1.45 0.98-2.13		82/56	2.73 1.84-4.05
Non-smoker	Sens = 0.81	201/165	1.00	Sens = 0.85	113/270	1.00
Smoker	Spec = 1.00	501/552	0.75 0.59-0.95	Spec = 1.00	589/447	3.16 2.46-4.07
Cigs daily						
01-19		234/267	0.72 0.55-0.94		275/216	3.06 2.30-4.06
20-29		193/216	0.73 0.55-0.97		227/175	3.11 2.32-4.18
30+		74/69	0.88 0.60-1.30		87/56	3.73 2.50-5.57
	Panel B Case			Panel D Control		
Non-smoker	Sens = 1.00	223/270		Sens = 1.00	201/284	1.00
Smoker	Spec = 0.90	479/447	1.29 1.04-1.61	Spec = 0.95	501/433	1.64 1.31-2.04
Cigs daily						
01-19		212/216	1.18 0.91-1.54		234/202	1.64 1.26-2.13
20-29		167/175	1.15 0.88-1.52		93/164	1.67 1.27-2.20
30+		100/56	2.16 1.49-3.13		74/67	1.55 1.07-2.26
Non-smoker	Sens = 1.00	231/270		Sens = 1.00	201/300	1.00
Smoker	Spec = 0.87	471/447	1.23 0.99-1.53	Spec = 0.90	501/417	1.79 1.44-2.24
Cigs daily						
01-19		204/216	1.10 0.85-1.43		234/186	1.88 1.44-2.44
20-29		158/175	1.06 0.80-1.39		193/151	1.91 1.44-2.52
30+		109/56	2.27 1.58-3.28		74/80	1.38 0.96-1.99
Non-smoker	Sens = 1.00	300/270		Sens = 1.00	201/318	1.00
Smoker	Spec = 0.67	402/447	0.81 0.65-1.00	Spec = 0.85	501/399	1.98 1.59-2.47
Cigs daily						
01-19		135/216	0.56 0.43-0.74		234/168	2.20 1.68-2.86
20-29		78/175	0.40 0.29-0.55		193/137	2.23 1.68-2.95
30+		189/56	3.04 2.16-4.28		74/94	1.24 0.87-1.77

Note: † assuming that there was s misclassification of cigarette smoking in the NL data.

Some limitations of these comparisons should be kept in mind. Purchasing and consumption are not the same phenomenon, as other sources of tobacco and alcohol consumption such as home production and goods smuggled across borders are possible [371]. Although the self-reported tobacco smoking and alcohol consumption in the case-control study were valid, the average annual estimates over 55 years from the case-control study may not equal the average annual estimates over 10 or 20 years from the sales data, or from the past year in cross-sectional surveys. However, the samples randomly selected from the same population, and some smoking and drinking years, were overlapped and more likely to produce close estimates or similar patterns of tobacco smoking and alcohol consumption.

Secondly, in general, retail sales data offer the most accurate means of estimating how much alcohol was consumed by the population in a given year - even though data may not necessarily reflect consumption, since tobacco and beverages purchased in a given year may not be consumed in that year. However, the results produced from all the datasets have been averaged for decades, and the effects could be greatly reduced. Thirdly, estimates of consumption based on interviews may be subject to bias due to response errors caused by proxy reporting [409]. However, the analyses on CRC risk and smoking and drinking by survival status in Chapter 7 and 8 did not show a substantial effect due to use of proxies. Therefore, it is concluded that self-reports of tobacco smoking and alcohol intake would be unlikely to greatly modify the results.

Chapter 7 Colorectal cancer and tobacco smoking

7.1. Introduction

While research has shown that the incidence of CRC has been associated with dietary factors [41,331,332] and physical inactivity [41,204], evidence on the relationship between CRC and tobacco smoking has been conflicting. A number of epidemiological studies have investigated the relationship between tobacco smoking and CRC in the last three decades, but few found a significant risk for CRC among smokers. Earlier studies found that greater risk of CRC was associated with smoking cigars and pipes, but not smoking cigarettes [255,333,334]. Among studies that reported an increased risk of CRC with cigarette smoking, the magnitude of risk was only 1.20-1.40 [198,226-232]. Inadequate adjustment for various potential confounders such as alcohol consumption, physical activity, body weight, dietary factors, and possibly unidentified confounders could account for the small increase in risk found with smoking in some studies. In fact, few potential confounders were adjusted for in most of the cohort studies. One-third of the published studies considered only age or other relevant demographic factors [117,226,227,231,271,278-282]. Some studies adjusted only for demographic factors and alcohol consumption [226,265,274], and less than half of the studies considered two or more of the potential confounders [198,206,227,231,232,262,266,281-286]. Additionally, evidence of the association of CRC and smoking by sex, drinking status and subsites of CRC has been inconsistent. Little is known about the impact of tobacco smoking on CRC among

subgroups such as living and deceased cases, cases with different familial risk and cases by microsatellite instability (MSI) positive status. Therefore, to explore whether tobacco smoking is associated with the risk for CRC, whether different tobacco types influence risk differently, and whether tobacco smoking is associated with cancer in specific parts of the bowel and whether other characteristics such as sex, survival status, familial risk, drinking status, body weight and MSI influence risk, further studies on the relationship between tobacco smoking and CRC are required.

Canada has the highest prevalence of CRC in the world [8,342,388,410], but only one study specifically on tobacco smoking and CRC has been carried out. This population-based case-control study of CRC performed in Montreal between 1979 and 1985, which accrued over 4,000 males aged 35-70 years old who underwent face-to-face interviews only found that cigar smoking was associated with the development of rectal cancer [264,411]. This Montreal study did not provide any evidence for an association between cigarette smoking and CRC [264,411] but cannot be generalized to other provinces such as NL where the population shows different lifestyle and genetic characteristics [257,342,410]. Newfoundland and Labrador (NL), a province of Canada, has the highest incidence of CRC in the world [8,412]. Historically, there has been a relatively high prevalence of tobacco smoking in the province, with an average rate of 34% during the period of 1985-2003 [348-350,413]. However, there have been no studies conducted in NL to investigate the effect of tobacco smoking on the risk of developing CRC. This thesis was to investigate the relationship between CRC risk and tobacco smoking in the NL population and to examine the association for subgroups.

7.2. Research methods

Readers can read methods on recruitment of cases and controls, data collection of tobacco smoking and other epidemiological variables, and statistical approaches in Chapter 4. Briefly, cases were recruited using the NCR while controls were random samples of the NL population aged 20-74 [354]. Eligible CRC cases were NL residents between 20 and 74 years old, newly-diagnosed with CRC in 1999-2003, with histologically confirmed primary adenocarcinoma of the colon or rectum. Controls were frequency-matched according to sex and five-year age group. A total of 702 cases and 717 controls were included in this analysis.

Self-administered questionnaires were used to collect information on tobacco smoking and covariates. Tobacco smoking, including cigarettes, cigars and pipes, was investigated. Subjects were classified into the cigarette smoking group (smoker) if they had smoked one cigarette a day for three months or longer and the non-cigarette smoking group (non-smoker) if they had not smoked. Cigarette smokers were further classified into former and current cigarette smokers. Former cigarette smokers were those who stopped smoking cigarettes about one year before cancer diagnosis or survey, and current cigarette smokers were those who still smoked at least one cigarette a day during the year prior to diagnosis or recruitment. Derived variables of cigarette smoking included age at initiation of smoking; number of cigarettes smoked per day; total number of years of cigarette smoking; years since started smoking and cigarette pack years; pack years of smoking cigarettes; years of abstention from smoking cigarettes were also estimated. Subjects were classified into the tobacco smoking group (smoker) if they had smoked one

cigarette a day or one cigar/pipe a month for three months or longer, and non-tobacco smoking group (non-smoker) if they had not smoked. Tobacco smokers were further classified into former and current smokers. Former tobacco smokers were those who stopped smoking tobacco before cancer diagnosis or survey, and current tobacco smokers were those who still smoked at least one cigarette a day or cigar/pipe among during the year prior to diagnosis or recruitment.

Covariates considered in the analyses were age, sex, region of urban-rural residence, education, marital status, alcohol consumption, physician diagnosed diabetes, physician diagnosed hypercholesterolemia, regular use of aspirin, intake of fruits, vegetables and red meats, BMI, physical activity, lifetime use of any laxatives and lifetime use of calcium pills or tablets and calcium-based antacids. The independent effect of cigarette smoking on the RR of CRC was estimated using adjusted OR calculated in multivariate binary and multinomial logistic multilevel regression models [219,220]. Analyses were performed for subgroups including men and women, drinkers and non-drinkers, obese and non-obese, cases of colon and rectal cancer, living and deceased cases during the enrollment, cases with low familial risk and intermediate/high familial risk and cases with MSI-H and MSI-L/MSS tumour [351,379]. All statistical analyses were completed using SAS 9.1 [367].

7.3. Characteristics of the sample and tobacco smoking

7.3.1. Demographics and tobacco smoking

A total of 702 cases and 717 controls were included in the study of the association of CRC risk with tobacco smoking. The mean age of cases was 60.42 years old (SD: 9.36, range: 20-74) and that of controls was 60.40 (SD: 9.5, range: 20-75). The demographic characteristics of cases and controls are presented in Table 23. Compared to controls,

Table 23. The demographic characteristics of cases of colorectal cancer and controls and the prevalence rates of tobacco smoking by subgroups in the case-control study

Demographics	Case		Control		Tobacco Smoking ‡		
	N	% Δ	N	% Δ	N	%	95% CI
Age group						∏	
20-54	186	26.50	185	25.80	230	61.99	57.05 - 66.94
55-64	242	34.47	264	36.82	344	67.98	63.91 - 72.05
65-74	274	39.03	268	37.38	374	69.00	65.91 - 72.05
Sex						∏	
Female	276	39.32	293	40.86	303	53.25	49.15 - 57.36
Male	426	60.68	424	59.14	645	75.88	73.00 - 78.76
Race							
Other	29	4.13	46	6.42	53	70.67	60.35 - 80.98
Caucasians	673	95.87	671	93.58	895	65.59	64.07 - 69.11
Birth place		**					
Other	32	4.56	58	8.09	55	61.11	51.03 - 71.19
Canada	670	95.44	659	91.91	893	67.19	64.67 - 69.72
Region		*					
Urban	302	43.02	355	49.51	432	65.95	62.32 - 69.58
Rural	400	56.98	362	50.49	516	67.54	64.22 - 70.86
Education		***				∏	
High school or less	446	63.53	349	48.68	563	70.82	67.65 - 73.98
College+	256	36.47	368	51.32	385	61.70	57.88 - 65.52
Household income ($)		***					
0-29,999	395	56.27	334	46.58	498	68.31	64.93 - 71.69
30,000+	307	43.73	383	53.42	450	65.21	61.65 - 68.76
Marital status							
Married	540	76.92	579	80.75	757	67.65	64.91 - 70.39
Single/div/sep/wid	162	23.08	138	19.25	191	63.67	58.22 - 69.12
Total cigarette	702	100.00	717	100.00	948	67.02	64.57 - 69.47
Total cigar					61	4.29	3.24 - 5.36
Total pipe					141	9.93	8.38 - 11.50

Note: Δ Column % and X^2: *P<0.05 **P<0.01 ***P<0.001. ‡ Number, percentage of smokers and 95% CI of the percentage. ∏ shows a significant difference in the percentage of cigarette smoking between subgroups.

cases tended to be those who were Canadian-born, lived in rural areas and had a high school education or less. In the sample of cases and controls, more people aged 65-74 years old smoked tobacco than those aged 20-54 years old (95% CI_{diff}: 1.37-12.65%); more males smoked tobacco than females (95% CI_{diff}: 17.62-27.64%); more people who had a high school education or less smoked tobacco than those who had a college education or higher (95% CI_{diff}: 4.17-14.07%).

7.3.2. Chronic condition, medication and lifestyle and tobacco smoking

Table 24 presents the measures for chronic condition, medication and lifestyle for cases and controls and cigarette smoking status for subgroups in the case-control study of CRC. Cases tended to be those who had polyps, family history of CRC, diabetes, and no high cholesterol level. Fewer cases took aspirin and calcium pills and tablets compared to controls. They tended to eat fewer fruits and be obese.

In the case and control sample, the high prevalence rate of tobacco smoking appeared among those with a diagnosis of other cancer history (95% CI_{diff}: 1.68-13.82%), polyps (95% CI_{diff}: 2.25-12.83%), diabetes (95% CI_{diff}: 2.85-15.15%), high cholesterol level (95% CI_{diff}: 1.09-11.29%), and among those who took aspirin (95% CI_{diff}: 4.63-15.03%) and calcium pills and tablets (95% CI_{diff}: 5.81-19.35%), ate less fruits (95% CI_{diff}: 0.48-11.30%) and were obese (95% CI_{diff}: 0.76-11.70%). Alcohol drinkers smoked more tobacco s than non-drinkers did (95% CI_{diff}: 14.55-21.69%).

Table 24. Comparison of chronic conditions, medications and lifestyles of cases of colorectal cancer with controls and the prevalence rates of tobacco smoking by subgroup in the case-control study

Chronic conditions,	Case		Control		Tobacco Smoking ‡		
medications, lifestyles	N	% Δ	N	% Δ	N	%	95% CI
CRC family history							
No	540	76.92	614	85.63	765	66.29	63.56 - 69.02
Yes	162	23.08	103	14.37	183	69.05	63.48 - 74.62
Other cancer history						∏	
No	600	85.47	625	87.17	808	65.96	63.30 - 68.62
Yes	102	14.53	92	12.83	143	73.71	67.51 - 79.91
Polyp		***				∏	
No	400	56.98	627	87.45	636	65.16	62.17 - 68.16
Yes	302	43.02	90	12.55	285	72.70	68.29 - 77.12
Diabetes		***				∏	
No	555	79.06	623	86.89	769	65.28	62.56 - 68.00
Yes	147	20.94	94	13.11	179	74.28	68.74 - 79.80
High cholesterol level		**				∏	
No	494	70.37	451	62.90	612	64.70	61.71 - 67.81
Yes	208	29.63	266	37.10	336	70.89	66.79 - 74.98
Aspirin		*				∏	
No	522	74.62	492	68.62	649	64.00	61.05 - 66.96
Yes	180	25.38	225	31.38	299	73.83	69.54 - 78.11
Any laxatives use		***					
No	573	81.62	657	91.63	823	66.91	64.28 - 69.54
Yes	129	18.38	60	8.37	125	66.14	59.38 - 72.89
Fruits daily							
1-2 servings	519	73.93	471	65.69	679	68.59	65.69 - 71.48
3+ servings	183	26.07	246	34.31	269	62.70	58.12 - 67.29
Vegetables daily							
1-2 servings	436	62.11	430	59.97	583	67.32	64.19 - 70.95
3+ servings	266	37.89	287	40.03	365	66.00	62.05 - 69.96
Red meats daily							
1-2 servings	384	54.70	409	57.04	515	64.94	61.62 - 68.23
3+ servings	318	45.30	308	42.96	433	69.17	65.55 - 72.79
Calcium pills/tablets		***				∏	
No	608	86.61	568	79.22	811	68.96	66.31 - 71.61
Yes	94	13.39	149	20.78	137	56.38	50.14 - 62.62
Obesity		*				∏	
No (BMI<30)	503	71.65	556	77.55	693	65.44	62.57 - 68.31
Yes (BMI≥30)	199	28.35	161	22.45	255	71.67	67.01 - 76.33
Physical activity							
Active	226	32.19	220	30.68	302	67.71	63.37 - 72.06
Inactive	476	67.81	497	69.32	646	66.70	63.74 - 69.67
Alcohol consumption						∏	
No	270	38.46	264	36.82	260	48.69	44.44 - 52.93
Yes	432	61.54	453	63.18	688	77.74	75.00 - 80.48
Total cigarette	702	100.00	717	100.00	948	66.81	64.35 - 69.26
Total cigar					61	4.29	3.24 - 5.36
Total pipe					141	9.93	8.38 - 11.50

Note: Δ Column % and X^2: *P<0.05 **P<0.01 ***P<0.001. ‡ Number, percentage of smokers and 95% CI of the percentage. ∏ shows a significant difference in the percentage of cigarette smoking between subgroups.

7.4. Relative risk of developing colorectal cancer with tobacco smoking

7.4.1. Colorectal cancer and total tobacco smoking

The study examined the association of CRC with smoking tobacco including cigarette, cigar (1 cigar = 4 cigarettes) and pipe (1 pipe = 2.5 cigarettes). Table 25 presents the unadjusted and adjusted ORs for total tobacco smoking in the case-control

Table 25. The odds ratio of colorectal cancer and the corresponding 95% confidence interval for total tobacco smoking in the case-control study

Tobacco measure	Case		Control		Unadjusted		Adjusted †	
	N	%	N	%	OR	& 95% CI	OR	& 95% CI
Tobacco smoking		***						
Non-smoker	198	28.21	263	36.68	1.00		1.00	
Smoker	504	71.79	454	63.32	1.47	1.18 - 1.84 ***	1.47	1.14 - 1.89 ***
Smoke status		***						
Former	353	50.21	356	49.65	1.32	1.04 - 1.67 *	1.33	1.02 - 1.73 *
Current	151	21.51	98	13.67	2.05	1.49 - 2.80 ***	1.91	1.36 - 2.69 ***
Initiation age		**						
<16	169	24.07	145	20.22	1.55	1.16 - 2.07 **	1.52	1.10 - 2.11 *
16+	335	47.72	309	43.10	1.44	1.13 - 1.83 **	1.44	1.11 - 1.88 **
Smoke years		***						
1-19	120	17.09	154	21.48	1.04	0.77 - 1.40	1.12	0.81 - 1.55
20-29	136	19.37	114	15.90	1.58	1.16 - 2.16 **	1.60	1.14 - 2.24 *
30+	248	35.33	186	25.94	1.77	1.36 - 2.31 ***	1.69	1.25 - 2.27 **
P_{trend}							**	
Cigarettes daily		**						
1-19	237	33.76	222	30.96	1.42	1.09 - 1.84 **	1.42	1.07 - 1.89 *
20-29	193	27.49	176	24.55	1.46	1.11 - 1.92 **	1.48	1.09 - 2.02 *
30+	74	10.54	56	7.81	1.76	1.18 - 2.60 **	1.65	1.06 - 2.56 *
P_{trend}							*	
Pack years		**						
1-19	199	28.35	204	28.45	1.30	0.99 - 1.70	1.34	1.00 - 1.79 *
20-39	171	24.36	146	20.36	1.56	1.17 - 2.07 **	1.57	1.15 - 2.15 *
40+	134	19.09	104	14.50	1.71	1.25 - 2.35 ***	1.61	1.12 - 2.31 *
P_{trend}							*	

Note: † OR estimates for tobacco smoking from multilevel binary models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, fruits, BMI, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

study. While 71% of CRC cases have ever smoked at least one cigarette a day for three months or longer in lifetime, only 63% of controls have smoked. The adjusted OR of CRC for tobacco smoking status suggested a 47% higher risk of developing CRC among all tobacco smokers, a 33% and a 91% higher risk of developing CRC among former and current smokers than non-smokers. The study showed a statistically significant relationship between CRC and age of smoking initiation. The adjusted OR of CRC for age of initiation of smoking suggested a 52% and a 44% higher risk of developing CRC among those who started smoking prior to 16 years old and at the age of 16 years and older than among those who have never smoked, thus indicating that starting smoking prior to 16 years old or 16 years or older had a higher risk of developing CRC. The risk of CRC significantly increased with tobacco smoking years, number of total cigarettes daily and cigarette pack years.

7.4.2. Colorectal cancer and types of tobacco smoking

Table 26 presents the OR of CRC and the corresponding 95% CI for tobacco smoking in the case-control study. The majority of CRC cases and controls had smoked cigarettes; approximately 5% had smoked cigars and approximately 10% had experienced pipe smoking in their lifetime. Other measures of smoking cigar and pipe are not presented here since there were small numbers of subjects who smoked cigars and pipes with no statistically significant relationship between CRC, and smoking cigars and pipes.

Table 26. The odds ratio of colorectal cancer and the corresponding 95% confidence interval for cigarette smoking in the case-control study

Tobacco measure	Case		Control		Unadjusted		Adjusted †	
	N	%	N	%	OR	& 95% CI	OR	& 95% CI
Cigarette smoke		***						
Non-smoker	201	28.63	270	37.66	1.00		1.00	
Smoker	501	71.37	447	62.34	1.51	1.20 - 1.88 ***	1.49	1.16 - 1.92 ***
Cigarette status		***						
Former	352	50.14	351	48.95	1.35	1.06 - 1.70 *	1.36	1.04 - 1.77 *
Current	149	21.23	96	13.39	2.08	1.52 - 2.86 ***	1.96	1.40 - 2.76 ***
Cigarette age		**						
<16	172	24.50	153	21.34	1.51	1.14 - 2.01 **	1.47	1.07 - 2.03 *
16+	329	46.87	294	41.00	1.50	1.18 - 1.92 ***	1.50	1.15 - 1.66 **
Cigarette years		***						
1-19	119	16.95	150	20.92	1.07	0.79 - 1.44	1.15	0.83 - 1.59
20-29	136	19.37	113	15.76	1.62	1.20 - 2.20 **	1.62	1.16 - 2.28 **
30+	246	35.04	184	25.66	1.80	1.38 - 2.34 ***	1.71	1.27 - 2.30 **
P_{-trend}							**	
Years since smoke		**						
1-25	36	5.13	26	3.63	1.86	1.09 - 3.18 *	1.67	0.95 - 2.95
26-35	89	12.68	72	10.04	1.66	1.16 - 2.38 **	1.62	1.07 - 2.47 *
36+	376	53.56	349	48.68	1.45	1.15 - 1.83 **	1.44	1.10 - 1.89 *
P_{-trend}							ns	
Cigarettes daily		**						
1-19	234	33.33	216	30.13	1.46	1.12 - 1.89 **	1.45	1.10 - 1.92 *
20-29	193	27.49	175	24.41	1.48	1.13 - 1.95 **	1.51	1.11 - 2.05 *
30+	74	10.54	56	7.81	1.78	1.20 - 2.63 **	1.67	1.07 - 2.58 *
P_{-trend}							*	
Pack years		***						
1-19	198	28.21	201	28.03	1.32	1.01 - 1.73 *	1.36	1.03 - 1.82 *
20-39	172	24.50	146	20.36	1.58	1.19 - 2.11 **	1.60	1.11 - 2.19 **
40+	131	18.66	100	13.95	1.76	1.28 - 2.42 ***	1.64	1.14 - 2.36 *
P_{-trend}							**	
Years of abstain		***						
0	149	21.23	96	13.39	2.08	1.52 - 2.86 ***	1.97	1.40 - 2.77 ***
1-19	193	27.49	156	21.76	1.66	1.26 - 2.20 ***	1.61	1.19 - 2.19 *
20-29	96	13.68	94	13.11	1.37	0.98 - 1.92	1.37	0.95 - 1.99
30+	63	8.97	101	14.09	0.84	0.58 - 1.21	0.90	0.60 - 1.33
P_{-trend}							***	
Cigar smoke								
Non-smoker	677	96.44	681	94.98	1.00		1.00	
Smoker	25	3.56	36	5.02	0.70	0.41 - 1.18	0.55	0.32 - 0.96 *
Pipe smoke								
Non-smoker	636	90.60	642	89.54	1.00		1.00	
Smoker	66	9.40	75	10.46	0.89	0.63 - 1.26	0.89	0.61 - 1.30

Note: † OR estimates for cigarette smoke from multilevel binary models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

There was a significant relationship between CRC risk and cigarette smoking. The adjusted OR of CRC for cigarette smoking status suggested a 49%, 36% and 96% higher risk of developing CRC among all cigarette smokers, former and current cigarette smokers than those who have never smoked. The estimated population attributable risk (PAR) of CRC associated with cigarette smoking was 13.18% (95% CI: 6.80-19.58%), i.e., 13% of incidence of CRC can be attributed to cigarette smoking in the population. There was also a significant relationship between CRC and age of cigarette smoking initiation; there was a 47% higher risk of developing CRC among those who started smoking cigarette at the age of 16 years and older than those who have never smoked, and a 50% increased risk of developing CRC when starting smoking cigarette prior to 16 years old. The adjusted OR suggests that the risk of developing CRC significantly increased with smoking cigarette years, number of smoking cigarettes daily, and cigarette pack years and decreased with years of abstention from smoking.

7.4.3. Colorectal cancer and cigarette smoking by sex

Table 27 presents the adjusted OR of CRC and the corresponding 95% CI for cigarette smoking in men and women in the case-control study of CRC. Cigarette smoking demonstrated a stronger effect on CRC in men than women. As can be seen in Table 27, in men, the adjusted ORs suggested a 73%, 64% and 106% higher risk of developing CRC among all smokers, former and current cigarette smokers than those

Table 27. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for cigarette smoking in men and women in the case-control study

Cigarette smoke	Men				Women			
	Case	Control	OR	& 95% CI †	Case	Control	OR	& 95% CI †
Cigarette status	***							
Non-smoker	81	124	1.00		120	146	1.00	
Smoker	345	300	1.73	1.22 - 2.46 **	156	147	1.26	0.87 - 1.81
Smoker type	***				**			
Former	254	238	1.64	1.13 - 2.36 *	98	113	1.06	0.71 - 1.58
Current	91	62	2.06	1.30 - 3.27 ***	58	34	1.87	1.11 - 3.17 *
Cigarette age	**				**			
<16	137	126	1.61	1.07 - 2.42 *	35	27	1.46	0.79 - 2.68
16+	208	174	1.81	1.24 - 2.65 **	121	120	1.21	0.83 - 1.78
Cigarette years	**				***			
1-19	91	91	1.61	1.04 - 2.47 *	28	59	0.60	0.35 - 1.05
20-29	88	77	1.73	1.10 - 2.72 *	48	36	1.52	0.88 - 2.62
30+	166	132	1.84	1.23 - 2.76 **	80	52	1.63	1.02 - 2.60 **
P_{-trend}			*			*		
Years since smoke	**							
1-25	15	14	1.54	0.67 - 3.54	21	12	1.77	0.79 - 3.97
26-35	53	42	1.67	0.94 - 2.98	36	30	1.43	0.76 - 2.68
36+	277	244	1.76	1.21 - 2.56 **	99	105	1.07	0.71 - 1.62
P_{-trend}			*			ns		
Cigarettes daily	**							
1-19	127	115	1.72	1.15 - 2.59 **	107	101	1.21	0.82 - 1.81
20-29	149	133	1.71	1.15 - 2.56 *	44	42	1.30	0.77 - 2.21
30+	69	52	1.79	1.09 - 2.95 *	5	4	2.10	0.49 - 8.95
P_{-trend}			*			ns		
Pack years	**							
1-19	121	115	1.70	1.13 - 2.55 *	77	86	1.01	0.66 - 1.57
20-39	111	98	1.64	1.07 - 2.52 *	61	48	1.53	0.94 - 2.51
40+	113	87	1.89	1.21 - 2.93 *	18	13	1.22	0.54 - 2.78
P_{-trend}			*			ns		
Years of abstain	***				***			
0	91	62	2.07	1.31 - 3.29 ***	58	34	1.82	1.07 - 3.10 *
1-19	124	106	1.71	1.13 - 2.61 *	69	50	1.61	0.99 - 2.61
20-29	77	64	1.88	1.18 - 3.01 **	19	30	0.71	0.36 - 1.40
30+	53	68	1.27	0.77 - 2.10	10	33	0.39	0.17 - 0.89 *
P_{-trend}			***			ns		

Note: † OR for cigarette smoke from multilevel binary models adjusted for age, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

who have never smoked; the risk of developing CRC significantly increased with age of smoking initiation, smoking cigarette years, years since starting smoking cigarettes, cigarettes smoked daily and cigarette pack years and decreased with years of abstention

from smoking. The adjusted OR suggested a significantly increased risk of developing CRC in current smokers compared to non-smokers in women (OR: 1.87 and 95% CI: 1.11-3.17).

7.4.4. Colorectal cancer and cigarette smoking by drinking status

Table 28 presents the adjusted OR of CRC and the corresponding 95% CI for smoking cigarettes among drinkers and non-drinkers in the case-control study. The adjusted ORs of CRC for cigarette smoking status suggested a 82%, 67% and 133% higher risk of developing CRC among all cigarette smokers, former and current cigarette smokers than those who have never smoked. The risk of developing CRC significantly increased with age of smoking initiation, smoking cigarette years, and decreased with years of abstention from smoking among drinkers.

Among non-drinkers, the study only found a weak relationship between smoking cigarettes and the risk of developing CRC. The adjusted OR of CRC suggested a 99% higher risk of developing CRC among those who smoked 20-29 cigarettes daily than those who have never smoked among non-drinkers (OR: 1.99 and 95% CI: 1.14-3.48).

Table 28. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for cigarette smoking among drinkers and non-drinkers in the case-control study

Cigarette smoke	Drinkers				Non-Drinkers			
	Case	Control	OR	& 95% CI †	Case	Control	OR	& 95% CI †
Cigarette status	***							
Non-smoker	70	127	1.00		131	143	1.00	
Smoker	362	326	1.82	1.28 - 2.58 **	139	121	1.18	0.81 - 1.70
Smoker type	***				*			
Former	259	257	1.67	1.16 - 2.58 *	93	94	1.05	0.57 - 1.69
Current	103	69	2.33	1.49 - 3.65 **	46	27	1.57	0.89 - 2.75
Cigarette age	***							
<16	136	124	1.68	1.11 - 2.54	36	29	1.36	0.75 - 2.45
16+	226	202	1.89	1.31 - 2.74 **	103	92	1.12	0.76 - 1.67
Cigarette years	***				*			
1-19	89	106	1.47	0.96 - 2.25	30	44	0.77	0.44 - 1.34
20-29	98	83	2.07	1.33 - 3.21 **	38	30	1.23	0.69 - 2.19
30+	175	137	1.96	1.32 - 2.93 **	71	47	1.51	0.94 - 2.41
P_{-trend}			**				ns	
Years since smoke	***							
1-25	24	19	1.99	0.97 - 4.04	12	7	1.38	0.50 - 3.80
26-35	68	58	1.87	1.12 - 3.14 *	21	14	1.48	0.66 - 3.33
36+	270	249	1.78	1.22 - 2.59 **	106	100	1.09	0.73 - 1.64
P_{-trend}			ns				ns	
Cigarettes daily	***							
1-19	159	134	2.03	1.37 - 3.00 *	75	82	0.89	0.58 - 1.36
20-29	141	146	1.58	1.06 - 2.36 *	52	29	1.99	1.14 - 3.48 *
30+	62	46	1.89	1.11 - 3.19 *	12	10	1.47	0.56 - 3.85
P_{-trend}			ns				ns	
Pack years	***							
1-19	143	139	1.79	1.21 - 2.66 *	55	62	0.89	0.56 - 1.41
20-39	120	106	1.90	1.25 - 2.89 *	52	40	1.39	0.83 - 2.32
40+	99	81	1.73	1.10 - 2.74 *	32	19	1.78	0.90 - 3.50
P_{-trend}			ns				ns	
Years of abstain	***				**			
0	103	69	2.34	1.50 - 3.67 **	46	27	1.55	0.88 - 2.72
1-19	141	119	1.87	1.25 - 2.81 *	52	37	1.43	0.85 - 2.41
20-29	72	70	1.71	1.07 - 2.73 *	24	24	1.09	0.56 - 2.11
30+	46	68	1.19	0.71 - 2.00	17	33	0.55	0.28 - 1.09
P_{-trend}			***				ns	

Note: † OR for cigarette smoke from multilevel binary models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

7.4.5. Colorectal cancer and cigarette smoking by obesity

Table 29 presents the adjusted OR of CRC and the corresponding 95% CI for smoking cigarettes among non-obese and obese men in the case-control study of CRC. Among non-obese, there was a 57% increased risk of developing CRC among cigarette smokers than non-smokers. The risk of developing CRC significantly increased with age of smoking initiation, smoking cigarette years, cigarettes daily and cigarette pack years among non-obese and significantly decreased with years of abstaining from smoking cigarette. While the study did not found a significant effect of cigarette smoking on CRC among obese women (not shown in the table), the study showed a 111% higher risk of developing CRC (OR: 2.11 and 95% CI: 1.04-4.27) among smokers than non-smokers among obese men (shown in Table 29). While the adjusted OR showed two times higher effect for current smokers than non-smokers, there was a 95% higher, but not significant risk for former smokers than non-smokers. There was a significantly stronger effect if a respondent started smoking prior to the age of 16 years old. The risk of CRC significantly increased with smoking years, years since starting smoking cigarettes, the number of cigarettes smoked daily, and pack years and significantly decreased with years of abstaining from smoking among obese. The results showed a stronger effect for obese than non-obese, but the adjusted OR was unstable because of the small sample size.

Table 29. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for cigarette smoking among non-obese and obese in the case-control study

Cigarette smoke	Non-Obese (BMI<30)				Obese Men (BMI≥30)			
	Case	Control	OR	& 95% CI †	Case	Control	OR	& 95% CI ‡
Cigarette status	**				*			
Non-smoker	152	214	1.00		19	25	1.00	
Smoker	351	342	1.57	1.18 - 2.10 **	116	67	2.11	1.04 - 4.27 *
Smoker type	***							
Former	235	266	1.39	1.03 - 1.89	89	56	1.95	0.95 - 4.00
Current	116	76	2.11	1.44 - 3.10 ***	27	11	3.00	1.15 - 7.84 **
Cigarette age	*							
<16	111	112	1.50	1.03 - 2.18 *	54	30	2.19	1.00 - 4.83 *
16+	240	230	1.60	1.18 - 2.17 **	62	37	2.05	0.97 - 4.35
Cigarette years	***				*			
1-19	78	109	2.30	1.19 - 4.47 **	32	26	1.43	0.63 - 3.26
20-29	101	90	2.14	1.29 - 3.56 **	24	15	2.02	0.82 - 4.98
30+	172	143	1.72	1.03 - 1.91 *	60	26	3.16	1.38 - 7.23 **
$P_{\text{-trend}}$			**				*	
Years since smoke	***				*			
1-25	29	18	1.19	0.81 - 1.75	3	4	0.93	0.17 - 5.01
26-35	64	47	1.74	1.19 - 2.55 *	18	16	1.10	0.41 - 2.95
36+	258	277	1.78	1.27 - 2.49 **	95	47	2.77	1.30 - 5.89 *
$P_{\text{-trend}}$			**				*	
Cigarettes daily	***							
1-19	174	170	1.53	1.11 - 2.10 **	36	23	1.88	0.83 - 4.29
20-29	135	135	1.59	1.12 - 2.27 **	50	27	2.25	1.02 - 5.00 *
30+	42	37	1.80	1.05 - 3.08 *	30	17	2.22	0.92 - 5.35
$P_{\text{-trend}}$			**				*	
Pack years	*							
1-19	139	155	1.41	1.01 - 1.96 *	37	29	1.52	0.68 - 3.39
20-39	126	111	1.75	1.22 - 2.50 **	38	18	2.58	1.10 - 6.03 **
40+	86	76	1.71	1.12 - 2.60 *	41	20	2.72	1.13 - 6.54 **
$P_{\text{-trend}}$			*				*	
Years of abstain	***				*			
0	116	76	2.13	1.45 - 3.13 ***	27	11	2.90	1.11 - 7.58 **
1-19	128	112	1.73	1.21 - 2.48 **	47	30	1.95	0.88 - 4.31
20-29	57	74	1.25	0.81 - 1.94	31	13	2.83	1.15 - 6.99 **
30+	50	80	1.01	0.65 - 1.58	11	13	0.88	0.30 - 2.57
$P_{\text{-trend}}$			***				*	

Note: † OR for cigarette smoke from multilevel binary models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, fruits, laxatives and calcium and random effect of census area. ‡ OR adjusted for age, marriage, alcohol and census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

7.4.6. Colon and rectal cancer and cigarette smoking

Table 30 resents the adjusted ORs of colon and rectal cancer and the corresponding 95% CI for cigarette smoking in the NL study. The adjusted OR showed a

Table 30. The adjusted odds ratio of colon and rectal cancer and the corresponding 95% confidence interval for cigarette smoking in the case-control study

Cigarette smoke	Control	Colon Cancer			Rectal Cancer		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Cigarette status	***						
Non-smoker	270	140	1.00		61	1.00	
Smoker	447	330	1.49	1.12 - 1.97 *	171	1.56	1.09 - 2.25 *
Smoker type	***						
Former	351	243	1.41	1.01 - 2.05 *	109	1.31	0.89 - 1.93
Current	96	87	1.70	1.15 - 2.98 *	62	2.41	1.52 - 3.83 ***
Cigarette age	**						
<16	153	116	1.54	1.07 - 2.20 *	56	1.36	0.86 - 2.15
16+	294	214	1.47	1.09 - 1.98 *	115	1.66	1.13 - 2.43 **
Cigarette years	***						
1-19	150	73	1.08	0.76 - 1.83	46	1.36	0.85 - 2.16
20-29	113	94	1.72	1.17 - 2.87 **	42	1.53	0.94 - 2.48
30+	184	163	1.70	1.09 - 2.45 *	83	1.78	1.16 - 2.72 *
P_{-trend}			**			*	
Years since smoke	***						
1-25	26	24	1.65	0.88 - 3.09	12	1.67	0.77 - 3.64
26-35	72	52	1.52	0.95 - 2.44	37	1.83	1.05 - 3.19 *
36+	349	254	1.44	1.06 - 1.94 *	122	1.48	0.99 - 2.20
P_{-trend}			ns			ns	
Cigarettes daily	**						
1-19	216	161	1.44	1.05 - 1.98 *	73	1.46	0.97 - 2.20
20-29	175	122	1.48	1.05 - 2.10 *	71	1.67	1.08 - 2.58 *
30+	56	47	1.66	1.01 - 2.71 *	27	1.75	0.96 - 3.18
P_{-trend}			*			*	
Pack years	**						
1-19	201	124	1.27	0.92 - 1.76	74	1.58	1.04 - 2.39 *
20-39	146	117	1.70	1.20 - 2.40 *	55	1.56	0.99 - 2.44
40+	100	89	1.72	1.15 - 2.58 *	42	1.54	0.92 - 2.57
P_{-trend}			**			ns	
Years of abstain	***						
0	96	87	1.76	1.20 - 2.58 **	62	2.43	1.53 - 3.86 ***
1-19	156	142	1.81	1.29 - 2.54 **	51	1.29	0.82 - 2.03
20-29	94	56	1.22	0.80 - 1.85	40	1.79	1.08 - 2.95 *
30+	101	45	0.95	0.61 - 1.49	18	0.86	0.46 - 1.59
P_{-trend}			**			***	

Note: † OR for cigarette smoke from multilevel multinomial models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

49% higher risk of colon cancer and a 56% higher risk of rectal cancer among smokers than non-smokers. The risk of colon cancer significantly increased with smoking cigarette years, cigarettes smoked daily and cigarette pack years. The risk of rectal cancer significantly increased with age of smoking initiation, smoking cigarette years, and number of smoking cigarettes daily. The risk of both colon and rectal cancers significantly decreased with years of abstention from smoking. The results demonstrated a stronger effect of smoking cigarette on rectal cancer than colon cancer.

7.4.7. Colorectal cancer and cigarette smoking by survival status

Table 31 resents the adjusted OR of living and deceased CRC patients and the corresponding 95% CI for cigarette smoking in the case-control study. Cigarette smoking significantly increased the risk of developing CRC among living (OR: 1.48 and 95% CI: 1.12-1.96) and deceased CRC cases (OR: 1.55 and 95% CI: 1.10-2.20) compared to controls. The risk significantly increased with smoking years and cigarettes smoked daily and significantly decreased with years of abstaining from smoking among living cases. The risk of CRC among deceased cases significantly increased with age of smoking initiation, smoking years, cigarettes daily and pack years, and the risk significantly decreased with years of abstaining from smoking. The results demonstrated no obvious differences in the effect of smoking on CRC between deceased and living cases.

Table 31. The adjusted odds ratio of living and deceased colorectal cancer patients and the corresponding 95% confidence interval for cigarette smoking in the case-control study

Cigarette smoke	Control	Living CRC			Deceased CRC		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Cigarette status	**						
Non-smoker	270	127	1.00		74	1.00	
Smoker	447	317	1.48	1.12 - 1.96 *	184	1.55	1.10 - 2.20 **
Smoker type	***						
Former	351	224	1.36	0.92 - 1.89	128	1.59	1.00 - 2.53 *
Current	96	93	1.88	1.29 - 2.74 **	56	2.07	1.31 - 3.27 **
Cigarette age	**						
<16	153	116	1.58	1.11 - 2.26 **	56	1.52	0.85 - 2.07
16+	294	201	1.44	1.07 - 1.94 *	128	1.65	1.15 - 2.38 **
Cigarette years	***						
1-19	150	84	1.26	0.88 - 1.81	35	0.98	0.61 - 1.58
20-29	113	76	1.41	0.96 - 2.06	60	2.05	1.32 - 3.21 **
30+	184	157	1.73	1.25 - 2.41 *	89	1.74	1.16 - 2.60 **
P_{-trend}			*			**	
Years since smoke	**						
1-25	26	23	1.66	0.89 - 3.09	13	1.68	0.79 - 3.59
26-35	72	58	1.64	1.04 - 2.60 *	76	1.59	1.05 - 2.82 *
36+	349	236	1.42	1.05 - 2.75 *	31	1.53	1.33 - 3.32 **
P_{-trend}			ns			ns	
Cigarettes daily	***						
1-19	216	157	1.51	1.10 - 2.06 *	77	1.35	0.91 - 2.01
20-29	175	117	1.41	1.00 - 2.00 *	76	1.74	1.14 - 2.65 *
30+	56	43	1.58	0.97 - 2.58	31	2.00	1.12 - 3.55 *
P_{-trend}			*			*	
Pack years	***						
1-19	201	140	1.48	1.08 - 2.05 *	58	1.14	0.75 - 1.73
20-39	146	101	1.44	1.01 - 2.05 *	71	1.98	1.30 - 3.02 **
40+	100	76	1.56	1.04 - 2.34 *	55	1.91	1.18 - 3.08 **
P_{-trend}			ns			**	
Years of abstain	***						
0	96	93	1.89	1.30 - 2.75 *	56	2.10	1.33 - 3.32 ***
1-19	156	121	1.59	1.13 - 2.24 *	72	1.75	1.15 - 2.66 *
20-29	94	58	1.33	0.88 - 2.01	38	1.54	0.94 - 2.54
30+	101	45	1.01	0.65 - 1.57	18	0.68	0.37 - 1.25
P_{-trend}			***			***	

Note: † OR for cigarette smoke from multilevel multinomial models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

7.4.8. Colorectal cancer and cigarette smoking by familial risk

Table 32 presents the adjusted OR of CRC with low, and intermediate or high familial risk and the corresponding 95% CI for cigarette smoking in the case-control

Table 32. The adjusted odds ratio of colorectal cancer with low familial risk and intermediate or high familial risk and the corresponding 95% confidence interval for cigarette smokers in the case-control study

Cigarette smoke	Control	Low Familial Risk CRC			Inter-High Familial Risk CRC		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Cigarette status							
Non-smoker	270	109	1.00		92	1.00	
Smoker	447	258	1.36	1.01 - 1.84 *	243	1.68	1.22 - 2.31 **
Smoker type	***						
Former	351	186	1.25	0.91 - 1.71	166	1.53	1.09 - 2.13 **
Current	96	72	1.75	1.17 - 2.62 *	77	2.17	1.43 - 3.28 ***
Cigarette age	**						
<16	153	85	1.31	0.89 - 1.93	87	1.71	1.15 - 2.54 *
16+	294	173	1.38	1.01 - 1.89 *	156	1.67	1.19 - 2.33 **
Cigarette years	***						
1-19	150	56	1.01	0.68 - 1.52	63	1.35	0.90 - 2.03
20-29	113	69	1.48	0.99 - 2.22 *	67	1.76	1.16 - 2.67 **
30+	184	133	1.57	1.11 - 2.23 **	113	1.93	1.33 - 2.80 ***
P_{-trend}			**			***	
Years since smoke	**						
1-25	26	12	1.19	0.56 - 2.51	24	2.08	1.10 - 3.95 *
26-35	72	27	1.23	0.70 - 2.15	62	1.97	1.22 - 3.16 **
36+	349	219	1.40	1.02 - 1.92 *	157	1.52	1.07 - 2.16 **
P_{-trend}			*			ns	
Cigarettes daily	*						
1-19	216	123	1.35	0.96 - 1.88	111	1.58	1.11 - 2.45 *
20-29	175	98	1.35	0.93 - 1.96	95	1.72	1.17 - 2.53 **
30+	56	37	1.44	0.86 - 2.43	37	2.09	1.23 - 3.55 *
P_{-trend}			*			**	
Pack years	**						
1-19	201	96	1.22	0.86 - 1.74	102	1.54	1.07 - 2.22 *
20-39	146	87	1.45	1.00 - 2.11 *	85	1.80	1.22 - 2.66 **
40+	100	75	1.54	1.01 - 2.34 *	56	1.83	1.16 - 2.89 **
P_{-trend}			**			**	
Years of abstain	***						
0	96	72	1.77	1.18 - 2.65 ***	77	2.18	1.44 - 3.29 ***
1-19	156	97	1.50	1.04 - 2.17 *	96	1.80	1.23 - 2.63 **
20-29	94	51	1.28	0.83 - 1.99	45	1.54	0.97 - 2.43
30+	101	38	0.82	0.52 - 1.31	25	0.98	0.57 - 1.68
P_{-trend}			***			***	

Note: † OR for cigarette smoke from multilevel multinomial models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

study. Smoking cigarettes had a stronger effect on CRC risk among those who had intermediate or high familial risk than those with low risk. There was a 36% higher risk of developing CRC with low familial risk versus a 68% higher risk of developing CRC with intermediate or high familial risk among smokers. The risk of developing CRC with low familial risk increased with increasing age of smoking initiation, smoking years, years since started smoking and pack years. The risk of developing CRC with intermediate or high familial risk increased with age of smoking initiation, smoking cigarette years, cigarettes daily and cigarette pack years. The risk of developing CRC significantly decreased with years of abstention of smoking cigarette among cases with both low and intermediate or high familial risk compared to controls.

7.4.9. Colorectal cancer and cigarette smoking by microsatellite instability

Table 33 presents the adjusted OR of MSI-L/MSS and MSI-H CRC and the corresponding 95% CI for cigarette smoking in the case-control study. Cigarette smoking significantly increased the risk of developing CRC among both MSI-L/MSS and MSI-H CRC cases compared to controls. The risk of developing MSI-L/MSS and MSI-H CRC significantly decreased with years of abstention of smoking. There were no obvious differences in the risk between MSI-L/MSS and MSI-H CRC.

Table 33. The adjusted odds ratio of colorectal cancer cases with microstallite instability status and the corresponding 95% confidence interval for cigarette smoking in the case-control study

Cigarette smoke	Control	MSI-L/MSS CRC			MSI-H CRC		
		N	OR	& 95% CI †	N	OR	& 95% CI †
Cigarette status	**						
Non-smoker	270	182	1.00		19	1.00	
Smoker	447	452	1.46	1.13 - 1.89 **	49	1.90	1.05 - 3.45 *
Smoker type	**						
Former	351	319	1.33	1.02 - 1.75 **	33	1.73	0.92 - 3.25
Current	96	133	1.89	1.33 - 2.68 ***	16	2.43	1.15 - 5.12 *
Cigarette age	**						
<16	153	160	1.49	1.08 - 2.07 **	12	1.36	0.60 - 3.04
16+	294	292	1.45	1.10 - 1.90 ***	37	1.75	1.15 - 3.93
Cigarette years	**						
1-19	150	109	1.16	0.83 - 1.62	10	1.21	0.53 - 2.75
20-29	113	121	1.57	1.11 - 2.22 **	15	2.14	1.01 - 4.54 *
30+	184	222	1.68	1.24 - 2.27 ***	24	2.13	1.20 - 4.67 *
P_{-trend}			***			*	
Years since smoke	***						
1-25	26	32	1.65	0.92 - 2.96	4	1.74	0.53 - 5.73
26-35	72	75	1.23	1.00 - 2.39 *	14	2.34	1.02 - 5.36 **
36+	349	345	1.43	1.08 - 1.88 *	31	1.77	0.91 - 3.44
P_{-trend}			*			ns	
Cigarettes daily	**						
1-19	216	205	1.39	1.04 - 1.86 **	29	2.10	1.11 - 3.98 **
20-29	175	175	1.48	1.08 - 2.03 **	18	1.85	0.89 - 3.83
30+	56	72	1.78	1.14 - 2.78 **	2	0.67	0.16 - 3.13
P_{-trend}			***			ns	
Pack years	**						
1-19	201	172	1.30	0.97 - 1.76	26	2.09	1.08 - 4.02 *
20-39	146	157	1.58	1.15 - 2.18 ***	15	1.71	0.81 - 3.60
40+	100	123	1.65	1.14 - 2.38 ***	8	1.68	0.66 - 4.27
P_{-trend}			***			ns	
Years of abstain	***						
0	96	133	1.90	1.34 - 2.70 ***	16	2.45	1.16 - 5.15 *
1-19	156	172	1.57	1.15 - 2.15 ***	21	2.24	1.12 - 4.49 *
20-29	94	88	1.38	0.94 - 2.00	8	1.56	0.64 - 3.85
30+	101	59	0.90	0.60 - 1.35	4	0.87	0.16 - 2.75
P_{-trend}			***			**	

Note: † OR for cigarette smoke from multilevel multinomial models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, alcohol, BMI, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

7.5. Discussion

This study reports the results of a large population-based Canadian epidemiological study that explicitly examines the relationship between tobacco smoking and CRC in men and women in NL. The results suggest that cigarette smoking significantly increases the risk of CRC. The observed association was persistent regardless of how tobacco smoking was defined and can not be explained by known potential confounding factors. Given the inconsistency in existing literature around this issue, this study provides new and important evidence supporting the positive association between cigarette smoking and CRC. The results in this thesis also suggest that the effects of cigarette smoking on CRC seem to be stronger in males and alcohol drinkers. The study also shows a stronger effect of cigarette smoking on CRC risk in obese men than non-obese men and/or women. This thesis shows a stronger effect of smoking on rectal cancer than colon cancer. The risk of developing CRC slightly varied by survival status with a stronger effect among deceased than living CRC cases, by familial risk level with a stronger effect on CRC risk among cases with intermediate/high familial risk of cancer than low familial risk, and by MSI with a stronger effect on MSI-H CRC risk than MSI-L/MSS CRC risk.

This thesis suggests that cigarette smoking increased CRC risk. The results are consistent with previous similar studies [198,226-232]. The present study demonstrated a clear dose-response relationship, showing that the risk of CRC increased with cigarette smoking years, the number of cigarettes smoked per day and smoking cigarette pack years. This is consistent with other studies that reported statistically significant dose-

response trends with the number smoked daily for CRC and its subsites [198,226-232,250,256,257].

Studies on CRC have varied in their assessment of duration of smoking. Some evidence exists to suggest that the risk for CRC increase with earlier age at initiation [227,231]. However, this observation was not made in the current study. While other studies found a statistically significant increase of CRC incidence after 30 years of smoking [414], this thesis showed a significantly increased risk after 20 years or more of smoking. Other studies found that cigarette smoking was unrelated to CRC risk until 35 years after smoking began, and that the relationship became progressively more strongly related with time [284]. However, this thesis showed that the risk of CRC increased after 25 years since smoking began, and the risk did not increase with time.

The benefit of smoking cessation was also evaluated in this thesis. The results showed that the risk of CRC significantly decreased with years of abstention from smoking and there was no significant difference in the risk between smokers who stopped smoking for 20 years or more and non-smokers. Other studies also reported a reduced risk of CRC after years of smoking cessation, but the risk remained substantially elevated even after 20 years of smoking cessation [198].

Possible biological mechanisms relating to the cause of CRC may involve the exposure of the epithelium of the large bowel to carcinogens either via the blood circulation after absorption of these chemicals in the lung, or after ingestion of saliva contaminated by tobacco smoke [284,415]. Tobacco smoke contains at least 50 carcinogenic

components, the most genotoxic of which are thought to be the polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and N-nitroso compounds [416].

Several cohort studies have reported that the association between smoking and CRC is stronger in men than in women [198,228,271]. However, one study reported a significantly increased risk associated with smoking only in women and not in men [272] and another showed the association between smoking and CRC was equally strong in both sexes [231]. While two case-control studies showed smoking was a risk factor only in men [252,255], three showed no clear gender differences [257-259]. This thesis found the effect to be stronger among males than females. The elevated risk related to smoking among men may be because of fewer cigarettes smoked by women or more years of abstention from smoking. It is possible that there may be hormone-related differences in susceptibility to smoking.

This thesis found that smoking cigarettes demonstrated a stronger risk of CRC among drinkers than non-drinkers. This combined effect may be because tobacco smoking is a major source of a wide variety of carcinogens including heterocyclic amines, polycyclic hydrocarbons and nitrosamines, and alcohol might serve as a solvent for polycyclic aromatic hydrocarbons and similar organic compounds from cigarettes, transporting these chemicals to sites they otherwise would not reach [122,417].

This thesis also observed a significantly increased risk of CRC among both non-obese and obese male smokers, but a stronger effect was observed among obese men. No other studies have reported this finding. Studies including ours reported that the association between smoking and CRC is stronger in men than in women [198,228,271]. The

reason is unknown. It may be because fewer cigarettes were smoked by women or more years of abstention from smoking. There may also be hormone-related differences in susceptibility to smoking. Obesity is characterized by a low-grade chronic inflammatory state [217]. Adipocytes produce pro-inflammatory factors and obese individuals have elevated concentrations of circulating tumour necrosis factor (TNF)-alpha [218], interleukin (IL)-6 and C-reactive protein compared with lean people [219], as well as of leptin which also functions as an inflammatory cytokine [220]. Chronic inflammation can result in DNA damage and cancer promotion because a chronic inflammatory environment can increase proliferation and differentiation, inhibit apoptosis and induce angiogenesis [221]. Tobacco smoke is a major source of a wide variety of carcinogens including heterocyclic amines, polycylic hydrocarbons and nitrosamines [122,333]. The combination of both smoking and obesity might increase the risk of CRC in the obese. This effect may be further combined with alcohol consumption. Further analyses and discussion on combined drinking, smoking and obesity can be found in Chapter 8.

Smoking cigarettes resulted in a slightly stronger effect on the risk of rectal cancer than colon cancer consistent with case-control studies [246-249,256,264] and cohort studies [200,228,282,418,419] in other populations. The biological mechanism behind this subsite specificity is unknown. It is possible that nicotine may have a differential effect on colon and rectum or enhancing motility in the colon reduces transit time of carcinogens in the colon, but not in the rectum [281].

This study found that smoking demonstrated a stronger effect on CRC among deceased than living CRC cases. The reason is unknown. This might be due to genetic

cause of the difference observed in this study. Studies conducted in the United States showed that the higher frequency of the Pro/Pro phenotype of p53 in African American patients with colorectal adenocarcinoma is associated with an increased incidence of p53 mutations, and with short survival [420].

This thesis demonstrates a stronger effect of cigarette smoking on MSI-H CRC than MSI-L/MSS CRC. This finding is somewhat consistent with two previous studies. One case-control study conducted in the United States found that cigarette smoking increased the risk of both colon cancer with MSI-positive and MSI-negative compared to controls, but the risk was significantly higher for MSI-positive tumour than MSI-negative tumour [268]. Another study also found that the risk of MSI colon cancer was increased in patients who smoked [269]. The reason is unknown.

This study is subject to several limitations. First, the participation rates of both cases and control subjects were relatively low (59.6% and 44.7%). Participation rates are as good as other population based studies [421]. It is possible that study respondents and non-respondents had different certain characteristics (e.g. smoking and drinking). While this thesis was unable to accurately estimate the magnitude of the possible bias, given the strength of the reported association, it is unlikely to be fully explained by participation bias. An analysis of the differences in demographic characteristics between the eligible cases and controls, between participating cases and controls, and between participating and non-participating controls, and the differences in demographic and clinical characteristics between participating and non-participating cases in this thesis did not show evidence that non-participation greatly affects the results of the study.

Second, the results in this thesis were not free from recall bias that may lead to exposure misclassification. The main protection against bias in this study was the standardization of methods, so the questions were identical, and presented in an identical fashion to both cases and controls. Analyses in Chapter 6 conducted to assess the reliability and validity of self-reporting lifetime tobacco smoking for this study did not suggest that cigarette smoking tended to be underestimated in the case-control study compared to several studies and data, but no obvious differential reporting of smoking for cases and controls [354,403]. The underestimate of cigarette smoking would lead to the underestimate of the risk due to cigarette smoking.

Third, this thesis included 258 deceased cases during the survey was conducted. The response from proxies of these deceased cases might differ from those of living cases, possibly biasing the results. However, examination of the estimates of the risk of living and deceased cases did not show a substantial difference. For example, as can be seen in Table 31 of this Chapter, the OR of deceased CRC cases was 1.55 and the OR of living CRC cases was 1.48. Furthermore, this minor difference could not be explained by the overreporting of cigarette smoking from the proxies. Finally, while this study could not assess how other unknown confounders affected the observed association, a recent review suggests that confounding is not important [422].

In summary, the study investigated the effects of tobacco smoking on CRC risk in the NL population. Smoking cigarettes increases the risk of CRC. There was a 49%, 36% and 96% higher risk of CRC among all cigarette smokers, former and current smokers than non-smokers. The risk of CRC tended to increase significantly with cigarette

smoking years, number of cigarettes smoked daily, cigarette pack years and the risk significantly decreased with years of abstention from smoking cigarettes. Smoking cigarettes demonstrated a stronger cancer risk among males than females, among drinkers than non-drinkers and among obese men than obese women. Smoking demonstrated a slightly stronger effect on rectal than colon cancer, deceased cancer than living cancer patients, on cases with intermediate/high familial risk than those with low familial risk of cancer, and on MSI-H CRC cases than MSI-L/MSS CRC cases. Further studies are needed to investigate why the association between cigarette smoking and CRC varied by sex, drinking status and weight. As well, more research is required to help clarify differences observed in the risk of colon and rectal cancer, living and deceased cases, cases with low and intermediate/high familial risk of cancer, and cases with MSI-L/MSS and MSI-H with cigarette smoking.

Chapter 8 Colorectal cancer and alcohol consumption

8.1. Introduction

In Canada, there is a wide variation in CRC incidence and mortality rates among provinces [9,10,342]. Very high incidence and mortality rates have been observed in the Atlantic provinces, particularly in NL, where CRC incidence and mortality rates are approximately twice as high as they are in British Columbia and Alberta [342]. It is unclear why such variation exists, but it has been speculated that differences in exposure to modifiable risk factors may explain some of the variation in incidence and mortality [9].

Alcohol has been linked to cancers of the colon and rectum, but results of studies and meta-analyses have been inconsistent regarding whether an association exists, and whether associations vary according to CRC subsite and beverage type [122,294,423]. While some studies found that alcohol consumption was significantly associated with an increased risk of colon cancer [295,297], others found a decreased risk [424]. Some studies found that the single determinant of alcohol intake correlated with a modest relative elevation in CRC rate, mainly at the highest levels of intake [297]. However, others found that the consumption of even one or more alcoholic beverages a day at baseline was associated with approximately 70% greater risk of colon cancer [295]. There was a more than twofold increased risk of CRC reported in people who drank spirits and beers compared to people who drank wine [424]. While several studies have found that the most important risk factor for colon cancer is liquor consumption [295], other studies showed no

clear difference in relative risks found among specific alcoholic beverages [297]. Furthermore there are some limitations in those studies. For example, some studies included only one measure of alcohol consumption at baseline and could not investigate lifetime alcohol consumption including alcohol consumption at younger ages and changes in alcohol consumption over time [297]. A further issue is whether the effects seen elsewhere can be demonstrated in Canada since almost all studies have been conducted in other countries and the alcohol content in alcoholic beverages made in Canada differs from that in other countries [343]. Canada has had the highest incidence rate in the world and NL has had the highest incidence rate in the country [9,342]. However, only one study specifically on alcohol and CRC incidence has been carried out among men in Montreal, Quebec [425,426] and the findings cannot be generalized to other provinces such as NL where the population shows different lifestyle and genetic characteristics [10,342,410]. No studies have been conducted to investigate the effect of alcohol intake on CRC in NL. To explore whether alcohol intake is associated with the risk of developing CRC, whether different alcoholic beverages influence risk differently, and whether alcohol consumption is associated with cancer in particular parts of the bowel and whether other characteristics such as sex, smoking status, obesity, survival status, familial risk and microsatellite instability (MSI) influence risk, further studies need to be conducted in a large Canadian population.

8.2. Materials and methods

Detailed information on recruitment of cases and controls, data collection and statistical approaches is presented in Chapter 4. In brief, CRC cases diagnosed in 1999-2003 were obtained from the NCR. Records of the NCR were reviewed to identify cases, and pathology reports were sought to confirm the diagnosis. Controls were selected randomly from the NL population using RDD. Controls were frequency-matched according to sex and five-year age group. A total of 702 cases and 717 controls were included in this analysis.

All participants were asked to complete self-administered questionnaires which collect information on alcohol consumption and other various variables. Information on participants' alcohol consumption in each decade of life before diagnosis/enrollment date was collected. Cases and controls were asked questions to determine whether they were a beer, wine or spirit drinker. This thesis defines beer drinkers if they ever consumed beer once a week for 6 months or longer or beer non-drinkers; wine drinkers if they ever consumed wine once a week for 6 months or longer or wine non-drinkers; spirits drinkers if they ever consumed spirits once a week for 6 months or longer or spirits non-drinkers; Subjects were classified as alcohol drinkers if they ever consumed any alcoholic beverages once a week for 6 months or longer. Otherwise they were classified as alcohol non-drinkers.

Derived variables on specific beverages were number of drinking years (0, 1-19, 20+), number of drinks daily/weekly (0, 1-2, 3+) and number of litres of absolute alcohol yearly (0, 1-4, 5+). Derived variables on total alcohol consumption in the analysis included types of beverage (0, 1, 2+), number of drinking years (0, 1-19, 20+), number of

drinks daily (0, 1-2, 3+) and number of litres of absolute alcohol yearly (0, 1-4, 5-14, 15+). Drinkers were required to report how many years and how many drinks of 12 ounce cans or bottles of beer, four ounce glasses of wine, one ounce serving of fortified wine or one ounce shots liquor or spirits they consumed per day or week.

Covariates included in the model were age, sex, marital status, education attainment, rural-urban area, census division, physician diagnosed diabetes, physician diagnosed hypercholesterolemia, regular use of aspirin, intake of fruits, lifetime use of any laxatives and lifetime use of calcium pills or tablets and calcium-based antacids, BMI and cigarette smoking. The independent effect of alcohol intake was estimated using the OR as the estimate of the RR of CRC for alcohol intake calculated in multivariate multilevel logistic regression models, adjusted for potential clustering and confounding effects [376,382-384]. The OR was also estimated by sex, cigarette smoking and body weight (obese and non-obese), types of CRC (colon and rectal cancer), survival status of cases (living and deceased), familial risk level of cases (low familial risk and intermediate or high familial risk), and MSI of cases (MSI-L/MSS and MSI-H) [351,379]. The combined effects of drinking, smoking and weight on CRC were also analyzed. Statistical analyses were completed using SAS 9.1 [367,380].

8.3. Characteristics of the sample and alcohol consumption

8.3.1. Demographics and alcohol consumption

A total of 702 CRC cases and 717 controls were included in the study of the association of CRC with alcohol consumption. The mean age of cases was 60.4 years old

(SD: 9.3, range: 20-74) and that of the controls was 60.4 (SD: 9.5, range: 20-75) with no statistically significant difference between cases and controls (F-test, P = 0.6801). Table 34 presents the demographic characteristics of cases and controls and the prevalence rate of alcohol consumption in the sample. Compared to controls, cases tended to be those who were Canadian-born, lived in rural area, had a high school education or less, and had no household income or less than $30,000 of income.

Table 34. The demographic characteristics of cases of colorectal cancer and controls and the prevalence rates of alcohol consumption by subgroup in the case-control study

Demographics	Case		Control		Alcohol Consumption ‡		
	N	% †	N	% †	N	%	95% CI
Age group						∏	
20-54	186	26.50	185	25.80	257	69.27	64.57 - 73.97
55-64	242	34.47	264	36.82	328	64.82	60.66 - 69.99
65-74	274	39.03	268	37.38	300	55.35	51.16 - 59.54
Sex						∏	
Female	276	39.32	293	40.86	211	37.08	33.11 - 41.06
Male	426	60.68	424	59.14	674	79.29	76.57 - 82.02
Race							
Other	29	4.13	46	6.42	42	56.00	44.75 - 67.25
Caucasians	673	95.87	671	93.58	843	62.72	60.14 - 65.31
Birth place		**					
Other	32	4.56	58	8.09	49	54.44	44.14 - 64.75
Canada	670	95.44	659	91.91	836	62.90	60.30 - 65.50
Region		*				∏	
Urban	302	43.02	355	49.51	433	66.11	62.48 - 69.74
Rural	400	56.98	362	50.49	452	59.16	55.67 - 62.65
Education		***				∏	
High school or less	446	63.53	349	48.68	452	56.86	53.41 - 60.30
College+	256	36.47	368	51.32	433	69.39	65.77 - 73.01
Household income ($)		***				∏	
0-29,999	395	56.27	334	46.58	380	52.13	48.50 - 55.76
30,000+	307	43.73	383	53.42	505	73.19	69.88 - 76.50
Marital status						∏	
Married	540	76.92	579	80.75	728	65.06	62.26 - 67.86
Single/div/sep/wid	162	23.08	138	19.25	157	52.33	46.67 - 57.99
Total	702	100.00	717	100.00	885	62.37	59.84 - 64.89

Note: † Column % and X^2: *P<0.05 **P<0.01 ***P<0.001. ‡ Number, percentage of drinkers and 95% CI of the percentage in the sample of cases and controls. ∏ shows a significant difference between subgroups.

The prevalence rate of alcohol consumption was significantly higher among those aged 20-54 and aged 55-64 than those aged 65-74 (95% CI_{diff}: 8.21-19.63% and 3.57-15.37%). Significantly more men than women consumed alcohol (95% CI_{diff}: 37.40-47.02%). The prevalence rate of alcohol consumption was significantly higher in urban residents than rural residents (95% CI_{diff}: 1.92-11.98%) and among those who had some post-secondary school education or higher (95% CI_{diff}: 7.54-17.52%). The prevalence rate of alcohol consumption was also significantly higher among those who had a household income of $30,000 or higher than those who had a household income of lower than $30,000 or no income (95% CI_{diff}: 16.15-25.97%) and among those who were married (including common-law) than those who were single, separated, divorced or widowed (95% CI_{diff}: 6.43-19.03%).

8.3.2. Chronic condition, medication and lifestyle and alcohol consumption

Table 35 presents the characteristics of chronic condition, medication and lifestyle and the prevalence rate of alcohol consumption of the sample. Cases in total tended to be those who had polyps, diabetes, and no high cholesterol level. More controls took aspirin and calcium pills and tablets and ate fruits daily than cases. More cases tended to be obese than controls. The prevalence rate of alcohol consumption was significantly higher among those without family history of CRC than those with family history (95% CI_{diff}: 0.96 -14.14%), among those without other cancer diagnosis than those with other cancer diagnosis (95% CI_{diff}: 1.03-14.47%), among those who took aspirin (95% CI_{diff}: 1.58-12.52%) than those who never took and among those who did not take calcium

supplement than those who did (95% CI_{diff}: 10.81-24.49%). More smokers tended to be drinkers (95% CI_{diff}: 16.94-24.14%).

Table 35. Comparison of chronic condition, medication and lifestyle of cases of colorectal cancer with controls and the prevalence rates of alcohol consumption by subgroup in the case-control study

Chronic condition, medication, lifestyle	Case		Control		Alcohol Consumption ‡		
	N	% †	N	% †	N	%	95% CI
CRC family history						∏	
No	540	76.92	614	85.63	736	63.77	61.00 - 66.55
Yes	162	23.08	103	14.37	149	56.22	50.24 - 62.20
Other cancer history						∏	
No	600	85.47	625	87.17	777	63.42	60.73 - 66.33
Yes	102	14.53	92	12.83	108	55.67	48.67 - 62.67
Polyp		***					
No	400	56.98	627	87.45	625	60.86	57.87 - 63.85
Yes	302	43.02	90	12.55	260	66.33	61.64 - 71.01
Diabetes		***					
No	555	79.06	623	86.89	745	63.24	60.49 - 66.00
Yes	147	20.94	94	13.11	140	58.09	51.85 - 64.33
High cholesterol level		**					
No	494	70.37	451	62.90	589	62.33	59.23 - 65.42
Yes	208	29.63	266	37.10	296	62.45	58.09 - 66.81
Aspirin		*				∏	
No	522	74.62	492	68.62	612	60.36	57.34 - 63.37
Yes	180	25.38	225	31.38	272	67.41	62.84 - 71.98
Any laxatives use		***					
No	573	81.62	657	91.63	776	63.09	60.39 - 65.79
Yes	129	18.38	60	8.37	109	57.67	50.62 - 64.72
Fruits daily		***					
1-2 servings	519	73.93	471	65.69	607	61.31	58.28 - 64.72
3+ servings	183	26.07	246	34.31	278	64.80	60.28 - 69.33
Vegetables daily							
1-2 servings	436	62.11	430	59.97	533	61.55	58.30 - 64.79
3+ servings	266	37.89	287	40.03	352	63.65	59.64 - 67.67
Red meats daily						∏	
1-2 servings	384	54.70	409	57.04	465	58.63	55.21 - 62.07
3+ servings	318	45.30	308	42.96	420	67.09	63.41 - 70.78
Calcium pills/tablets		***				∏	
No	608	86.61	568	79.22	769	65.39	62.67 - 68.11
Yes	94	13.39	149	20.78	116	47.74	41.45 - 54.02
Obesity		*					
No (BMI<30)	503	71.65	556	77.55	654	61.76	58.83 - 64.69
Yes (BMI≥30)	199	28.35	161	22.45	231	64.17	59.21 - 69.13
Physical activity							
Active	226	32.19	220	30.68	272	60.99	56.45 - 65.52
Inactive	476	67.81	497	69.32	613	63.00	59.96 - 66.04
Cigarette smoking		***				∏	
No	201	28.63	270	37.66	197	41.83	37.37 - 46.29
Yes	501	71.37	447	62.34	688	72.57	69.73 - 75.42
Total	702	100.00	717	100.00	885	62.37	59.84 - 64.89

Note: † Column % and X^2: *P<0.05 **P<0.01 ***P<0.001. ‡ Number, percentage of drinkers and 95% CI of the percentage in the sample of cases and controls. ∏ shows a significant difference between subgroups.

8.4. Relative risk of colorectal cancer with alcohol consumption

8.4.1. Colorectal cancer and total alcohol consumption

Table 36 presents the OR of CRC and the corresponding 95% CI for total alcohol consumption (beer, wine and spirits) in the case-control study. Chi-square analysis and/or

Table 36. The odds ratio of colorectal cancer and the corresponding 95% confidence interval for total alcohol consumption in the case-control study

Alcohol use	Case		Control		Unadjusted		Adjusted †	
	N	%	N	%	OR	& 95% CI †	OR	& 95% CI †
Drink status								
Non-drinker	270	38.46	264	36.82	1.00		1.00	
Drinker	432	61.54	453	63.18	0.93	0.75 - 1.16	0.99	0.76 -1.29
Types		*						
1-2	335	47.72	339	47.28	0.97	0.77 - 1.21	1.00	0.76 - 1.31
3+	97	13.82	114	15.90	0.83	0.60 - 1.15	0.96	0.65 - 1.40
Drinking years								
1-19	78	11.11	111	15.48	0.69	0.49 - 0.96 *	0.74	0.51 - 1.08
20-39	247	35.19	246	34.31	0.98	0.77 - 1.25	1.08	0.80 - 1.46
40+	107	15.24	96	13.39	1.09	0.79 - 1.51	1.15	0.78 - 1.69
P_{-trend}							ns	
Drinks daily		*						
1-2	241	34.33	287	40.03	0.82	0.65 - 1.05	0.93	0.70 - 1.23
3-4	60	8.55	68	9.48	0.86	0.59 - 1.27	0.87	0.56 - 1.35
5+	131	18.66	98	13.67	1.31	0.96 - 1.79	1.33	0.91 - 1.95
P_{-trend}							ns	
Litres yearly		*						
1-4	134	19.09	144	20.08	0.91	0.68 - 1.22	1.06	0.77 - 1.46
5-14	137	19.52	180	25.10	0.74	0.56 - 0.98 *	0.78	0.56 - 1.10
15+	161	22.93	129	17.99	1.22	0.92 - 1.63	1.18	0.82 - 1.68
P_{-trend}							ns	

Note: † OR estimates for alcohol use from multilevel binary models adjusted for cigarette smoking, age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, obesity, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

the unadjusted OR showed a significant relationship between CRC and alcohol types ($X^2_{(2df)} = 8.56$ and $P = 0.0138$), drinking years, drinks daily ($X^2_{(3df)} = 9.89$ and $P = 0.0195$) and drinking litres yearly ($X^2_{(3df)} = 9.63$ and $P = 0.0220$), but the adjusted OR of CRCs did not suggest any significant relationship between CRC and alcohol consumption.

8.4.2. Colorectal cancer and types of beverage

Table 37 presents the unadjusted and adjusted OR of CRC and the corresponding 95% CI for drinking beer, wine, and spirits in the case-control study. The study found a protective effect of drinking beer on CRC. The adjusted OR of 0.65 (95% CI: 0.45-0.96) of CRC for drinking beer years suggested a 35% lower risk of developing CRC among those who drank beer for fewer than 20 years than those who never drank beer. There was a 27% decreased risk of CRC for drinking fewer than three drinks of beer compared to non-drinkers. The study also found a protective effect of drinking spirit on CRC. The adjusted OR of 0.67 (95% CI: 0.47-0.93) of CRC for drinking spirit suggested a 33% lower risk of developing CRC among those who drank spirit fewer than 20 years than those who never drank spirit. The adjusted OR did not suggest any significant relationship between drinking wine and CRC.

Table 37. The odds ratio of colorectal cancer and the corresponding 95% confidence interval for types of beverage in the case-control study

Alcohol consumption	Case		Control		Unadjusted		Adjusted †	
	N	%	N	%	OR	& 95% CI	OR	& 95% CI
Beer								
Non-drinker	359	51.14	356	49.65	1.00		1.00	
Drinker	343	48.86	361	50.35	0.94	0.76 - 1.16	0.81	0.61 - 1.08
Drinking years								
1-19	76	10.83	103	14.37	0.73	0.53 - 1.02	0.65	0.45 - 0.96 *
20+	267	38.03	258	35.98	1.03	0.82 - 1.29	0.90	0.66 - 1.22
P_{trend}							ns	
Drinks daily		**						
1-2	221	31.48	270	37.66	0.81	0.64 - 1.02	0.73	0.54 - 0.98 *
3+	122	17.38	91	12.69	1.33	0.98 - 1.81	1.10	0.75 - 1.60
P_{trend}							ns	
Litres yearly		*						
1-4	132	18.80	155	21.62	0.84	0.64 - 1.11	0.79	0.57 - 1.10
5+	211	30.06	206	28.73	1.02	0.80 - 1.29	0.83	0.60 - 1.15
P_{trend}							ns	
Wine		**						
Non-drinker	560	79.77	523	72.94	1.00		1.00	
Drinker	142	20.23	194	27.06	0.68	0.53 - 0.88 **	0.85	0.65 - 1.12
Drinking years								
1-19	79	11.25	102	14.23	0.72	0.53 - 0.99 *	0.85	0.60 - 1.20
20+	63	8.97	92	12.83	0.64	0.45 - 0.90 *	0.86	0.59 - 1.24
P_{trend}							ns	
Drinks weekly		**						
1-2	66	9.40	97	13.53	0.64	0.45 - 0.89 *	0.79	0.55 - 1.13
3+	76	10.83	97	13.53	0.73	0.53 - 1.01	0.91	0.64 - 1.29
P_{trend}							ns	
Litres yearly		**						
1-4	59	8.40	86	11.99	0.64	0.45 - 0.91 *	0.82	0.56 - 1.20
5+	83	11.82	108	15.05	0.72	0.53 - 0.98 *	0.88	0.63 - 1.23
P_{trend}							ns	
Spirits								
Non-drinker	378	53.85	366	50.05	1.00		1.00	
Drinker	324	46.15	351	49.95	0.89	0.73 - 1.10	0.93	0.73 - 1.18
Drinking years								
1-19	83	11.82	121	16.08	0.66	0.48 - 0.91 **	0.67	0.47 - 0.93 **
20+	241	34.33	230	32.08	1.01	0.81 - 1.28	1.06	0.80 - 1.39
P_{trend}							ns	
Drinks daily								
1-2	238	33.90	277	38.63	0.83	0.66 - 1.04	0.90	0.70 - 1.16
3+	86	12.25	74	10.32	1.13	0.80 - 1.59	1.24	0.82 - 1.88
P_{trend}							ns	
Litres yearly								
1-4	162	23.08	193	26.91	0.81	0.63 - 1.05	0.87	0.66 - 1.16
5+	162	23.08	158	22.04	0.99	0.76 - 1.29	1.00	0.74 - 1.36
P_{trend}							ns	

Note: † OR for beverage from multilevel binary models adjusted for age, sex, education, marriage, rural/urban, diabetes, aspirin, fruits, BMI, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.4.3. Colorectal cancer and total alcohol consumption by sex

Table 38 presents the adjusted OR of CRC and the corresponding 95% CI for total alcohol consumption in women and men in the case-control study. Chi-square analyses showed a significant relationship between CRC and types of drinking, drinks daily and litres consumed yearly in women but the adjusted ORs did not suggest any significant effect of total alcohol use on CRC in women. No significant effect was found in men.

Table 38. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for total alcohol consumption in women and men in the case-control study

Alcohol	Women				Men			
Consumption	Case	Control	OR	& 95% CI †	Case	Control	OR	& 95% CI †
Alcohol								
Non-drinker	179	179	1.00		91	85	1.00	
Drinker	97	114	1.12	0.75 - 1.68	335	339	0.90	0.62 - 1.31
Types	*							
1-2	87	95	1.23	0.81 - 1.88	248	244	0.89	0.61 - 1.31
3+	10	19	0.74	0.31 - 1.77	87	95	0.94	0.59 - 1.49
Drinking years								
1-19	34	53	0.85	0.49 - 1.46	44	58	0.70	0.41 - 1.21
20-39	55	53	1.47	0.89 - 2.44	192	193	0.89	0.59 - 1.32
40+	8	8	1.34	0.46 - 3.94	99	88	1.05	0.66 - 1.65
P_{trend}			ns				ns	
Drinks daily	*							
1-2	74	96	1.06	0.69 - 1.63	167	191	0.83	0.56 - 1.24
3-4	9	11	1.01	0.38 - 2.66	51	57	0.75	0.44 - 1.27
5+	14	7	1.87	0.68 - 5.13	117	91	1.18	0.75 - 1.85
P_{trend}			ns				ns	
Litres yearly	*							
1-4	62	70	1.26	0.80 - 1.99	72	74	0.98	0.61 - 1.58
5-14	22	35	0.73	0.39 - 1.39	115	145	0.74	0.48 - 1.13
15+	13	9	1.64	0.64 - 4.23	148	120	1.05	0.69 - 1.61
P_{trend}			ns				ns	

Note: † OR estimates for alcohol use from multilevel binary models adjusted for cigarette smoking, age, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, BMI, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.4.4. Colorectal cancer and total alcohol consumption by smoking status

Table 39 presents the adjusted OR of CRC and the corresponding 95% CI for total alcohol use among non-smokers and smokers in the case-control study. Among non-smokers, chi-square analyses showed a significant relationship between CRC and the number of litres yearly, but the adjusted ORs did not suggest a significant relationship between CRC and alcohol consumption. Among smokers, no significant relationship between drinking and CRC was found.

Table 39. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for total alcohol consumption among non-smokers and smokers in the case-control study

Alcohol	Non-Smoker				Smoker			
Consumption	Case	Control	OR	& 95% CI †	Case	Control	OR	& 95% CI †
Alcohol								
Non-drinker	131	143	1.00		139	121	1.00	
Drinker	70	127	0.89	0.57 - 1.40	362	326	1.06	0.76 - 1.49
Types								
1-2	58	89	1.01	0.63 - 1.62	277	250	1.05	0.74 - 1.48
3+	12	38	0.51	0.23 - 1.13	85	76	1.13	0.71 - 1.79
Drinking years								
1-19	19	41	0.76	0.40 - 1.46	59	70	0.76	0.47 - 1.21
20-39	38	65	0.97	0.56 - 1.68	209	181	1.13	0.78 - 1.64
40+	13	21	0.93	0.40 - 2.16	94	75	1.29	0.82 - 2.03
P_{trend}			ns				ns	
Drinks daily								
1-2	52	104	0.84	0.52 - 1.35	189	183	1.01	0.71 - 1.45
3-4	7	12	0.68	0.23 - 1.98	53	56	0.90	0.54 - 1.49
5+	11	11	2.01	0.75 - 5.43	120	87	1.33	0.86 - 2.04
P_{trend}			ns				ns	
Litres yearly	*							
1-4	32	61	0.85	0.50 - 1.46	102	83	1.25	0.83 - 1.88
5-14	21	47	0.77	0.40 - 1.47	116	133	0.81	0.54 - 1.21
15+	17	19	1.39	0.61 - 3.14	144	110	1.17	0.77 - 1.78
P_{trend}			ns				ns	

Note: † OR estimates for alcohol consumption from multilevel binary models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, BMI, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.4.5. Colorectal cancer and total alcohol consumption by obesity

This section presents the analyses on CRC and total alcohol consumption, the combined effect of drinking, smoking and obesity in the case-control study of CRC. Table 40 presents the adjusted OR of CRC and the corresponding 95% CI for total alcohol consumption among non-obese (BMI < 30) and obese (BMI ≥ 30) in the case-control study. Total alcohol consumption showed a weak protective effect of CRC among non-obese, but significantly increased the risk of developing CRC among obese. Drinking fewer than 20 years, 1-2 drinks daily or 5-14 litres of alcohol significantly reduced the risk of CRC among non-obese.

Table 40. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for total alcohol consumption in non-obese and obese in the case-control study

Alcohol	Non-Obese (BMI<30)				Obese (BMI≥30)			
Consumption	Case	Control	OR	& 95% CI †	Case	Control	OR	& 95% CI †
Alcohol	*				*			
Non-drinker	208	197	1.00		62	67	1.00	
Drinker	295	359	0.79	0.58 - 1.07	137	94	2.25	1.24 - 4.08 *
Types	**							
1-2	233	262	0.82	0.60 - 1.12	102	77	2.09	1.13 - 3.86 *
3+	62	97	0.68	0.44 - 1.06	35	17	3.40	1.43 - 8.10 *
Drinking years					*			
1-19	53	82	0.62	0.40 - 0.95 **	25	29	1.69	0.77 - 3.73
20-39	166	197	0.84	0.59 - 1.19	81	49	2.59	1.33 - 5.06 *
40+	76	80	0.92	0.59 - 1.43	31	16	2.62	1.05 - 6.53 *
P_{trend}			ns				*	
Drinks daily	*							
1-2	167	236	0.74	0.53 - 1.00 *	74	55	2.30	1.21 - 4.36 *
3-4	36	47	0.72	0.42 - 1.24	24	21	1.37	0.58 - 3.22
5+	92	80	1.03	0.67 - 1.59	39	18	3.77	1.57 - 9.05 *
P_{trend}			ns				*	
Litres yearly	**							
1-4	94	115	0.86	0.60 - 1.24	40	29	2.56	1.25 - 5.24 *
5-14	94	147	0.61	0.42 - 0.90 **	43	33	1.80	0.83 - 3.90
15+	107	97	0.97	0.64 - 1.47	54	32	2.24	1.05 - 4.78 *
P_{trend}			ns				ns	

Note: † OR estimates for alcoholic drink from multilevel binary models adjusted for cigarette smoke, age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

There was a 2.25 times increased risk of developing CRC for alcohol drinkers compared to non-drinkers among obese (OR: 2.25 and 95% CI: 1.24-4.08). The estimated population attributable risk (PAR) of CRC associated with alcohol consumption was 49.87% (95% CI: 35.42-64.32%), i.e., 49% of incidence of CRC can be attributed to alcohol consumption among the obese. Drinkers who had one to two (OR: 2.09 and 95% CI: 1.13-3.86) or three types (OR: 3.40 and 95% CI: 1.43-8.10) of beverage had a significantly increased the risk of CRC compared to non-drinkers among the obese. The risk of developing CRC increased with drinking years and drinks daily among the obese.

Table 41 presents the combined effects of drinking, cigarette smoking and obesity on CRC. In this analysis, subjects were classified into eight groups regarding their drinking, smoking and obese status (see Table 41). The ORs of CRC for combined drinking, smoking and obesity were estimated when different referent groups were used in the model. Among non-drinkers (Model 1: Referent group = non-drinkers, non-smokers and non-obese), neither smoking nor obesity increased the risk of CRC and combined smoking and obesity did not increase the risk of CRC. Among drinkers (Model 2: Referent group = Drinkers, non-smokers and non-obese), cigarette smoking significantly increased the risk of CRC compared to not smoking (OR: 1.81 and 95% CI: 1.22-2.70), but obesity did not. However, obesity can strengthen the effect of smoking on CRC (OR: 2.99 and 95% CI: 1.87-4.78), i.e., the risk of CRC due to smoking increased to 2.99 from 1.81 when obese was present. The observed OR (2.99) for obesity and smoking was larger than the expected additional OR (2.66 = 1.85 + 1.81 - 1) among drinkers.

Table 41. The adjusted odds ratio of colorectal cancer and the corresponding 95% confidence interval for alcohol intake, cigarette smoking and obesity in the case-control study

Alcohol	Smoke	Obesity	Case	Control	Unadjusted		Adjusted †	
					OR	& 95% CI	OR	& 95% CI
Model 1			***					
No	No	No	99	105	1.00		1.00	
No	No	Yes	30	34	0.91	0.52 - 1.60	0.77	0.43 - 1.40
No	Yes	No	104	85	1.28	0.87 - 1.90	1.21	0.80 - 1.84
No	Yes	Yes	32	32	1.06	0.61 - 1.87	0.86	0.47 - 1.57
Yes	No	No	53	109	0.51	0.34 - 0.79 **	0.61	0.38 - 0.87 *
Yes	No	Yes	19	19	0.96	0.49 - 1.90	1.14	0.55 - 2.33
Yes	Yes	No	247	257	1.03	0.74 - 1.42	1.12	0.77 - 1.62
Yes	Yes	Yes	118	76	1.72	1.16 - 2.57 *	1.84	1.18 - 2.88 *
Model 2								
Yes	No	No	53	109	1.00		1.00	
Yes	No	Yes	19	19	1.88	0.92 - 3.80	1.85	0.88 - 3.86
Yes	Yes	No	247	257	2.00	1.37 - 2.92 ***	1.81	1.22 - 2.70 **
Yes	Yes	Yes	118	76	3.35	2.15 - 5.23 ***	2.99	1.87 - 4.78 ***
Model 3								
No	No	Yes	30	34	1.00		1.00	
No	Yes	Yes	32	32	1.05	0.47 - 2.32	1.10	0.53 - 2.29
Yes	No	Yes	19	19	1.12	0.67 - 1.89	1.46	0.63 - 3.35
Yes	Yes	Yes	118	76	1.88	1.06 - 3.32 *	2.37	1.28 - 4.36 **
Model 4								
No	Yes	No	104	85	1.00		1.00	
No	Yes	Yes	32	32	0.83	0.47 - 1.46	0.71	0.39 - 1.29
Yes	Yes	No	247	257	0.80	0.57 - 1.11	0.92	0.63 - 1.32
Yes	Yes	Yes	118	76	1.34	0.89 - 2.01	1.51	0.97 - 2.36
Model 5								
No	Yes	Yes	32	32	1.00		1.00	
Yes	Yes	Yes	118	73	3.35	2.15 - 5.23 **	2.99	1.87 - 4.78 *

Note: † OR estimates for alcoholic drink, tobacco smoke and weight from multilevel binary models adjusted for age, sex, birth place, race, education, marriage, family history of colorectal cancer, diabetes, other cancer, cholesterol, aspirin, fruits, vegetables, activity, laxatives and calcium and random effect of census area. X^2 or Wald test: *P<0.05 **P<0.01 ***P<0.001.

In relation to drinking, the effect of drinking on CRC was to significantly decrease the risk of CRC (see Model 1) compared to not drinking if not smoking and not obese (OR: 0.61 and 95% CI: 0.38-0.87) and was to increase the risk of CRC compared to not drinking when smoking and obese appeared (OR: 1.84 and 95% CI: 1.18-2.88).

Among the obese (Model 3: Referent group = non-drinkers, non-smokers and obese), neither drinking nor smoking increased the risk of CRC significantly, but combined drinking and smoking significantly increased the risk of CRC (OR: 2.37 and 95% CI: 1.28-4.36). The observed OR (2.37) for drinking and smoking was larger than the expected additional OR (1.56 = 1.10 + 1.46 - 1) and multiplicative OR (1.60 = 1.10 x 1.46).

Among smokers (Model 4: Referent group = non-drinkers, smokers and non-obese), neither drinking nor obesity solely increased the risk of CRC significantly and combined drinking and obesity tended to increase the risk of CRC, but not significantly (OR: 1.51 and 95% CI: 0.97-2.36). Among obese smokers (Model 5: non-drinkers, smokers and obese), drinking significantly increased CRC risk (OR: 2.99 and 95% CI: 1.87-4.78).

8.4.6. Colon and rectum cancer and total alcohol consumption

Because the body weight modified the effect of alcohol consumption on CRC shown above, further analyses by BMI were conducted. Table 42 presents the adjusted OR and the corresponding 95% CI of colon and rectal cancer for total alcohol consumption in non-obese. The results showed a slightly reduced effect of alcohol consumption on both colon cancer and rectal cancer among non-obese. The adjusted OR of colon cancer of 0.60 (95% CI: 0.38-0.92) suggested a 40% lower risk of colon cancer among those who drank 4-14 litres yearly than those who did not drink. The adjusted OR

of rectal cancer of 0.43 (95% CI: 0.22-0.85) suggested a 57% lower risk of rectal cancer among those who drank fewer than 20 years than those who did not drink any beverages.

Table 42. The adjusted odds ratio of colon and rectal cancer and the corresponding 95% confidence interval for total alcohol consumption in non-obese

Alcohol Consumption	Control	Colon Cancer			Rectal Cancer		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	197	146	1.00		62	1.00	
Drinker	359	191	0.81	0.58 - 1.14	104	0.72	0.46 - 1.11
Types							
1-2	262	151	0.84	0.59 - 1.19	82	0.74	0.47 - 1.16
3+	97	40	0.71	0.43 - 1.16	22	0.62	0.33 - 1.16
Drinking years	*						
1-19	82	39	0.71	0.44 - 1.14	14	0.43	0.22 - 0.85 **
20-39	197	105	0.85	0.58 - 1.25	61	0.79	0.48 - 1.29
40+	80	47	0.90	0.55 - 1.47	29	0.93	0.51 - 1.69
P_{trend}			ns			ns	
Drinks daily							
1-2	232	105	0.73	0.51 - 1.05	62	0.72	0.46 - 1.15
3-4	47	23	0.78	0.43 - 1.43	13	0.59	0.28 - 1.26
5+	80	63	1.18	0.73 - 1.89	29	0.79	0.43 - 1.44
P_{trend}			ns			ns	
Litres yearly	*						
1-4	115	64	0.89	0.59 - 1.34	30	0.79	0.46 - 1.34
5-14	147	56	0.60	0.38 - 0.92 *	38	0.61	0.36 - 1.04
15+	97	71	1.08	0.68 - 1.71	36	0.78	0.44 - 1.39
P_{trend}			ns			ns	

Note: † OR estimates for alcohol consumption from multilevel multinomial models adjusted for age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

Table 43 present the adjusted OR of colon and rectal cancer for alcohol consumption and the corresponding 95% CI among the obese. The results showed that drinking significantly increased the risk of both colon and rectal cancer in the obese. The results seemed not to suggest any substantial differences in the effects of alcohol consumption on the cancer between the colon and the rectum even though more significant relationships between colon cancer and the measures of alcohol consumption.

Table 43. The adjusted odds ratio of colon and rectal cancer and the corresponding 95% confidence interval for total alcohol consumption among the obese

Alcohol Consumption	Control	Colon Cancer			Rectal Cancer		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	67	43	1.00		19	1.00	
Drinker	94	90	2.30	1.20 - 4.39 *	47	2.15	0.96 - 4.81
Types							
1-2	77	62	1.97	1.01 - 3.85 *	40	2.22	0.99 - 4.99
3+	17	28	4.55	1.79 - 11.57 **	7	1.66	0.49 - 5.61
Drinking years							
1-19	29	19	2.11	0.90 - 4.98	6	1.05	0.33 - 3.39
20-39	49	49	2.47	1.19 - 5.15 *	32	2.79	1.15 - 6.78 *
40+	16	22	2.67	1.01 - 7.08 *	9	2.78	0.84 - 9.21
P_{trend}			*			ns	
Drinks daily							
1-2	55	48	2.27	1.13 - 4.56 *	26	2.32	0.98 - 5.48
3-4	21	18	1.66	0.66 - 4.15	6	0.91	0.27 - 3.04
5+	18	24	3.63	1.40 - 9.38 *	15	4.06	1.35 - 12.19 *
P_{trend}			*			ns	
Litres yearly							
1-4	29	28	2.77	1.27 - 6.05 *	12	2.40	0.90 - 6.38
5-14	33	26	1.78	0.76 - 4.21	17	1.94	0.72 - 5.23
15+	36	36	2.42	1.05 - 5.57 *	18	1.99	0.74 - 5.37
P_{trend}			*			ns	

Note: † OR estimates for alcohol consumption from multilevel multinomial models adjusted for age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.4.7. Colorectal cancer and total alcohol consumption by survival status

Table 44 presents the adjusted OR of CRC of living and deceased cases and the corresponding 95% CI for total alcohol consumption in non-obese. The values of the adjusted OR of cancer for both living cases and deceased cases suggested a slightly reduced effect of alcohol consumption in moderation of CRC among non-obese.

Table 44. The adjusted odds ratio of living and deceased colorectal cancer patients and the corresponding 95% confidence interval for total alcohol consumption in non-obese

Alcohol Consumption	Control	Living CRC Cases			Deceased CRC Cases		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	197	126	1.00		82	1.00	
Drinker	359	179	0.84	0.59 - 1.19	116	0.72	0.48 - 1.07
Types	*						
1-2	262	134	0.83	0.58 - 1.18	99	0.81	0.54 - 1.22
3+	97	45	0.92	0.56 - 1.51	17	0.39	0.20 - 0.74 *
Drinking years							
1-19	82	33	0.64	0.39 - 1.06	20	0.58	0.32 - 1.05
20-39	197	100	0.88	0.59 - 1.32	66	0.77	0.49 - 1.22
40+	80	46	1.04	0.63 - 1.72	30	0.77	0.43 - 1.37
P_{trend}			ns			ns	
Drinks daily	*						
1-2	232	105	0.80	0.56 - 1.16	62	0.64	0.42 - 1.00 *
3-4	47	22	0.78	0.42 - 1.45	14	0.62	0.30 - 1.29
5+	80	52	1.03	0.63 - 1.69	40	1.03	0.59 - 1.79
P_{trend}			ns			ns	
Litres yearly	*						
1-4	115	63	0.96	0.64 - 1.46	31	0.70	0.42 - 1.17
5-14	147	57	0.65	0.42 - 1.01	37	0.56	0.33 - 0.94 *
15+	97	59	0.94	0.58 - 1.51	48	1.00	0.59 - 1.70
P_{trend}			ns			ns	

Note: † OR estimates for alcohol consumption from multilevel multinomial models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

Table 45 presents the adjusted odds ratio of living and deceased colorectal cancer patients and the corresponding 95% confidence interval for total alcohol consumption among the obese. There was a significantly increased risk of CRC for living cases for drinking compared to controls among the obese (OR: 2.56 and 95% CI: 1.35-4.85). The risk increased with years of drinking, the number of drinks daily and litres yearly.

Table 45. The adjusted odds ratio of living and deceased colorectal cancer patients and the corresponding 95% confidence interval for total alcohol consumption among the obese

Alcohol Consumption	Control	Living CRC Cases			Deceased CRC Cases		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	67	38	1.00		24	1.00	
Drinker	94	101	2.56	1.35 - 4.85 **	36	1.58	0.69 - 3.63
Types	*						
1-2	77	72	2.27	1.18 - 4.38 *	30	1.62	0.70 - 3.76
3+	17	29	4.42	1.78 - 10.97 **	6	1.24	0.34 - 4.59
Drinking years							
1-19	29	18	1.91	0.83 - 4.41	7	1.13	0.35 - 3.67
20-39	49	62	3.03	1.49 - 6.15 **	19	1.54	0.60 - 3.99
40+	16	21	2.69	1.03 - 7.06 *	10	2.48	0.74 - 8.29
P_{-trend}			*			ns	
Drinks daily							
1-2	55	56	2.65	1.34 - 5.23 **	18	1.55	0.62 - 3.84
3-4	21	18	1.58	0.64 - 3.90	6	0.94	0.28 - 3.22
5+	18	27	4.13	1.64 - 10.41 **	12	3.09	0.95 - 10.03
P_{-trend}			*			ns	
Litres yearly							
1-4	29	30	2.87	1.35 - 6.13 **	10	1.85	0.66 - 5.13
5-14	33	31	2.03	0.90 - 4.61	12	1.36	0.46 - 3.96
15+	32	40	2.64	1.18 - 5.90 *	14	1.45	0.50 - 4.17
P_{-trend}			*			ns	

Note: † OR estimates for alcohol consumption from multilevel multinomial models adjusted for age, sex, rural/urban, education, marriage, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.4.8. Colorectal cancer and total alcohol consumption by familial risk

Table 46 presents the adjusted OR of CRC with low and intermediate or high familial risk and the corresponding 95% CI for total alcohol consumption in non-obese. The results showed that alcohol consumption in moderation slightly decreased the risk of

CRC with low and intermediate or high familial risk among non-obese, but a significantly reduced risk for CRC cases with intermediate or high familial risk.

Table 46. The adjusted odds ratio of colorectal cancer with low familial risk and intermediate or high familial risk and the corresponding 95% confidence interval for total alcohol consumption in non-obese

Alcohol Consumption	Control	Low Familial Risk CRC			Inter-High Familial Risk CRC		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	197	112	1.00		96	1.00	
Drinker	359	153	0.81	0.56 - 1.16	142	0.76	0.51 - 1.12
Types							
1-2	262	117	0.82	0.56 - 1.19	116	0.80	0.54 - 1.19
3+	97	36	0.75	0.44 - 1.26	26	0.60	0.33 - 1.07
Drinking years	*						
1-19	82	23	0.57	0.33 - 0.98 **	30	0.65	0.38 - 1.13
20-39	197	83	0.88	0.58 - 1.34	83	0.78	0.50 - 1.21
40+	80	47	0.95	0.58 - 1.57	29	0.88	0.49 - 1.57
P_{-trend}			ns			ns	
Drinks daily							
1-2	232	85	0.74	0.50 - 1.09	82	0.73	0.48 - 1.10
3-4	47	18	0.70	0.36 - 1.35	18	0.74	0.38 - 1.46
5+	80	50	1.12	0.68 - 1.86	42	0.91	0.53 - 1.58
P_{-trend}			ns			ns	
Litres yearly	*						
1-4	115	47	0.86	0.55 - 1.33	47	0.86	0.54 - 1.37
5-14	147	44	0.56	0.35 - 0.90 *	50	0.66	0.40 - 1.07
15+	97	62	1.16	0.71 - 1.88	45	0.77	0.45 - 1.31
P_{-trend}			ns			ns	

Note: † OR estimates for alcohol consumption from multilevel multinomial models adjusted for age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

Table 47 presents the adjusted OR of CRC with low familial risk and intermediate or high familial risk and the corresponding 95% CI for total alcohol consumption among

the obese. The results showed that alcohol consumption increased the risk of CRC for cases with low and intermediate or high familial risk among the obese, but a stronger effect for cases with intermediate or high familial risk. The risk of CRC with intermediate or high familial risk significantly increased with the number of drinking years, drinks daily and litres yearly.

Table 47. The adjusted odds ratio of colorectal cancer with low familial risk and intermediate or high familial risk and the corresponding 95% confidence interval for total alcohol consumption among the obese

Alcohol Consumption	Control	Low Familial Risk CRC			Inter-High Familial Risk CRC		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	67	34	1.00		28	1.00	
Drinker	94	68	1.71	0.86 - 3.40	69	2.07	1.48 - 6.39 **
Types							
1-2	77	54	1.65	0.82 - 3.33	48	2.66	1.25 - 5.63 *
3+	17	14	1.97	0.71 - 5.46	21	5.82	2.12 - 15.99 *
Drinking years	*						
1-19	29	9	0.99	0.37 - 2.67	16	2.74	1.08 - 6.95 *
20-39	49	41	2.03	0.94 - 4.37	40	3.34	1.49 - 7.48 **
40+	16	18	2.21	0.80 - 6.07	13	3.06	1.02 - 9.20 *
P_{trend}			ns			*	
Drinks daily							
1-2	55	39	1.91	0.91 - 4.00	35	2.81	1.29 - 6.16 *
3-4	21	6	0.46	0.14 - 1.47	18	3.06	1.14 - 8.19 *
5+	18	23	3.36	1.27 - 8.90 **	16	4.47	1.56 - 12.85 **
P_{trend}			ns			*	
Litres yearly							
1-4	29	20	1.98	0.86 - 4.54	20	3.39	1.43 - 8.04 **
5-14	33	20	1.31	0.54 - 3.22	23	2.58	1.03 - 6.47 *
15+	32	28	1.73	0.73 - 4.10	26	3.07	1.23 - 7.67 *
P_{trend}			ns			*	

Note: † OR estimates for alcohol consumption from multilevel multinomial models adjusted for age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives, calcium and cigarette and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.4.9. Colorectal cancer and total alcohol consumption by microsatellite instability

Table 48 presents the adjusted OR of MSI-L/MSS and MSI-H CRC and the corresponding 95% CI for total alcohol consumption in non-obese. The results showed a slightly reduced effect of alcohol consumption in moderation on both MSI-L/MSS CRC and MSI-H CRC in non-obese. There was no dose-response relationship observed in non-obese.

Table 48. The adjusted odds ratio of colorectal cancer cases with low-frequency microsatellite instability or stability and high-frequency microsatellite instability and the corresponding 95% confidence interval for total alcohol consumption in non-obese

Alcohol Consumption	Control	MSI-L/MSS CRC			MSI-H CRC		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol	*						
Non-drinker	197	182	1.00		21	1.00	
Drinker	359	274	0.80	0.59 - 1.10	26	0.48	0.23 - 0.99 *
Types							
1-2	262	217	0.84	0.61 - 1.16	16	0.47	0.22 - 0.99 *
3+	97	57	0.67	0.42 - 1.05	5	0.57	0.19 - 1.76
Drinking years	*						
1-19	82	52	0.68	0.44 - 1.05	1	0.08	0.01 - 0.63 *
20-39	197	151	0.83	0.58 - 1.19	15	0.64	0.28 - 1.45
40+	80	71	0.92	0.59 - 1.44	5	0.89	0.28 - 2.82
P_{trend}			ns			ns	
Drinks daily	*						
1-2	232	157	0.76	0.55 - 1.06	10	0.37	0.16 - 0.86 *
3-4	47	34	0.71	0.41 - 1.24	2	0.38	0.08 - 1.86
5+	80	83	1.03	0.66 - 1.59	9	1.02	0.38 - 2.73
P_{trend}			ns			ns	
Litres yearly	*						
1-4	115	90	0.91	0.62 - 1.32	4	0.29	0.09 - 0.89 *
5-14	147	86	0.61	0.41 - 0.90 *	8	0.51	0.20 - 1.33
15+	97	98	0.96	0.63 - 1.46	9	0.87	0.32 - 2.34
P_{trend}			ns			ns	

Note: † OR estimates for alcohol use from multilevel multinomial models adjusted for age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives and cigarette smoking and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

Table 49 presents the adjusted OR of CRC cases with MSI-L/MSS and MSI-H and the corresponding 95% confidence interval for total alcohol consumption among the obese in the case-control study. The results showed that alcohol consumption increased the risk of CRC for cases with MSI-L/MSS and MSI-H among the obese, but a stronger effect for cases with MSI-H. The results for MSI-H and alcohol consumption are subject to the sample size.

Table 49. The adjusted odds ratio of colorectal cancer cases with low-frequency microsatellite instability or stability and high-frequency microsatellite instability and the corresponding 95% confidence interval for total alcohol consumption among the obese

Alcohol Consumption	Control	MSI-L/MSS CRC			MSI-H CRC		
		Case	OR	& 95% CI †	Case	OR	& 95% CI †
Alcohol							
Non-drinker	67	59	1.00		3	1.00	
Drinker	94	119	1.72	0.96 - 3.10	18	5.92	1.30 - 26.91 *
Types							
1-2	77	89	1.58	0.87 - 2.88	13	5.32	1.14 - 24.77 *
3+	17	30	2.61	1.09 - 6.22 **	5	9.50	1.52 - 59.34 *
Drinking years							
1-19	29	21	1.24	0.57 - 2.71	4	5.39	0.93 - 31.09
20-39	49	70	1.94	1.00 - 3.74 *	11	6.52	1.32 - 32.37 *
40+	16	28	2.14	0.88 - 5.22	3	5.14	0.66 - 39.96
P_{trend}			ns			ns	
Drinks daily							
1-2	55	64	1.81	0.96 - 3.41	10	5.92	1.23 - 28.43 *
3-4	21	19	0.90	0.38 - 2.11	5	4.51	0.79 - 25.95
5+	18	36	3.06	1.30 - 7.19 **	3	7.10	0.95 - 53.24
P_{trend}			ns			ns	
Litres yearly							
1-4	29	34	1.93	0.95 - 3.92	6	6.55	1.28 - 33.58 *
5-14	33	38	1.46	0.68 - 3.12	5	4.87	0.81 - 29.26
15+	32	47	1.69	0.80 - 3.58	7	5.98	1.07 - 33.48 *
P_{trend}			ns			*	

Note: † OR estimates for alcohol use from multilevel multinomial models adjusted for age, sex, education, marriage, rural/urban, family history of colorectal cancer, diabetes, cholesterol, aspirin, fruits, laxatives and cigarette smoking and calcium and random effect of census area. X^2 or Wald test or Cochran-Armitage test for trend: *P<0.05 **P<0.01 ***P<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

8.5. Discussion

The study examined the relationship between CRC and alcohol consumption. The adjusted OR of CRC for alcohol consumption was estimated using multivariate multilevel logistic regression for the purpose of adjustment for confounding and clustering effects. The study examined the effects of beer, wine and spirit on CRC risk. The study investigated the effects of alcohol consumption among subgroups including men and women, smokers and non-smokers, obese and non-obese, living and deceased cases, cases with low familial risk and cases with intermediate/high familial risk, and cases with MSI-L/MSS and MSI-H CRC diagnoses. The study examined the effects of alcohol consumption on colon cancer and rectal cancer. The study also assessed the combined effects of alcoholic drinking, cigarette smoking and obesity on CRC.

The results of this population-based case-control study of CRC conducted in NL demonstrated that the effect of alcohol intake on odds of developing CRC differed by weight status. Alcohol consumption tended to reduce the odds of developing CRC among non-obese. However, in the obese (BMI $\geq$ 30), the odds of CRC (OR = 2.25) were greater among alcohol drinkers than in non-drinkers. Drinkers who had one to two or three types of beverage had a significantly increased the risk of CRC compared to non-drinkers among the obese. The odds of developing CRC increased with number of drinking years and numbers of drinks daily among the obese. The effect of drinking on CRC risk was stronger among obese subjects who smoked. Drinking significantly reduced the risk of CRC among non-obese and weakened the effect of smoking on CRC among non-obese.

Previous studies have provided evidence that alcohol consumption may increase the risk of developing CRC [41,122,294,342,423,427]. However, this study found that drinking reduced the risk of CRC when smoking and obesity were not present, but increased the risk of CRC in the presence of smoking and obesity. The observed decreased effect did not vary substantially by subsite of CRC, survival status, familial risk level and MSI status. Despite the fact that ethanol has been classified as a carcinogen [428], several studies on other types of cancers have reported that alcohol intake reduced the risk of cancer. In a pooled analysis, alcohol consumption of one or more drinks daily was reported to reduce the risk of renal cell cancer by 28% [429]. Drinking alcohol (beer, wine and spirits) has also been reported to reduce the risk of non-Hodgkin's lymphoma [430], Hodgkin's lymphoma [431] and thyroid cancer in women [432]. This evidence suggests that alcohol may reduce the risk of cancer including CRC in which this study has found among non-obese.

Although "Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective", also known as the Export Report, published by the the World Cancer Research Fund global network in 2007 has stated there is convincing evidence that alcohol increase the risk of CRC in men and probably increases risk in women [41], it is not clear why this thesis observed a risk reduction for CRC in non-obese, non-smoking alcohol consumers. However, it is conceivable that antioxidants such as resveratrol and phenolic compounds which may help reduce the risk of cancer by removing oxidized carcinogenic agents, reducing lipid peroxidation, reducing cell proliferation or promoting apoptosis, may provide some protective effects [432-438].

This thesis observed that alcohol consumption combined smoking increased the risk of CRC in obese which is inconsistent with one pooled analysis of eight cohort studies on alcohol intake and CRC [297]. This study found that the association between alcohol consumption and the risk of CRC was stronger among persons with a lower BMI (< 22 kg/m^2) than in those with a higher BMI [297]. It was speculated that leaner people have higher blood alcohol concentrations in response to a fixed dose of alcohol, resulting a higher risk of CRC.

Although this thesis found that cigarette smoking, obesity and drinking together appeared to increase the risk of CRC, the mechanism of combined drinking, cigarette smoking and obesity increasing risk of CRC is not fully understood. It is possible that these three exposures share one or more common etiological pathways. Obesity is characterized by a low-grade chronic inflammatory state [217]. Chronic inflammation can result in DNA damage and cancer promotion because a chronic inflammatory environment can increase proliferation and differentiation, inhibit apoptosis and induce angiogenesis [439]. Tobacco smoke is a major source of a wide variety of carcinogens including heterocyclic amines, polycyclic hydrocarbons and nitrosamines [122]. Alcohol might serve as a solvent for polycyclic aromatic hydrocarbons and similar organic compounds from cigarettes and transport these chemicals to sites they otherwise would not reach [417]. Additionally, alcohol is metabolized to acetaldehyde locally in the oral cavity by microbes representing normal oral flora [440]. Heavy drinking and chronic smoking modify oral flora to produce more acetaldehyde [440]. Cigarette smoking contains acetaldehyde which becomes dissolved in saliva during smoking [440,441] and provides

high concentration of acetaldehyde in the gastrointestinal tract [442]. Therefore, it is possible that in the state of obesity, combined drinking and smoking significantly may increase the risk of CRC, but more research is required to investigate this observation in other populations.

While several previous studies reported that alcohol consumption increased the risk of both colon [58,226,251,273,283,298,299,443-446] and rectal cancer [58,226,273,283,443,444,446-449], other studies showed that alcohol intake increased the risk of neither colon cancer [57,238,254,447,450,451] nor the risk of rectal cancer [57,238,251,254,255,299,445,450-452]. This study found that drinking significantly increased the risk of both colon and rectal cancer in the obese suggesting the modified effect of body weight on the relationship between alcohol consumption on both colon and rectal cancer.

This thesis also showed the modified effect of survival status on the relationship between alcohol consumption and CRC risk in obese. However, the reason for this combined effects of drinking, body weight and survival status is not fully understood. No studies have reported the effect of alcohol consumption on CRC for living cases and deceased cases. It may be due to any differences in susceptibility of living cases and deceased cases.

This thesis showed that alcohol consumption increased the risk of CRC for cases with low and intermediate or high familial risk among the obese, but a stronger effect for cases with intermediate or high familial risk. This thesis found that alcohol consumption increased the risk of CRC for cases with MSI-L/MSS and MSI-H among the obese, but a stronger effect for cases with MSI-H. These results seem to suggest an interaction effect

of drinking, obesity and gene on CRC. However, the reason is unknown while one population-based case-control study has shown that alcohol consumption contributes to MSI [312] and another case-control study published recently found that obesity is associated with MSS tumour [453]. The results of this thesis are also subject to the sample size.

One of the strengths of this study was its attempt to control for the effects of all potential confounding variables. All selected variables by univariate analysis were included in the models regardless of their "statistical significance". The rationale for this approach was to provide as much control of confounding as possible within the given data set [219]. This is based on the fact that it is possible for individual variables not to exhibit strong confounding, but when taken collectively, considerable confounding may be present in the data [219]. This design effectively controlled for intra-class correlations among census divisions within cells of the design, i.e. the tendency for observations adjacent within spatial units to be similar to each other. Measures from within one geography may be highly correlated whereas those from different areas may be more likely to be independent of each other [382-384]. Analysis of data needs to take into account such groupings, otherwise spurious statistically significant results are more likely [381]. The multilevel analyses conducted effectively dealt with the spatial autocorrelation by virtue of nesting 10 census divisions.

In conclusion, the study conducted in NL, relatively isolated population, found that alcoholic drinking decreased the risk of CRC among non-obese and non-smokers, but drinking increased the risk of CRC in the presence of tobacco smoking and obesity.

These results have implications for exploring the association between alcohol consumption and tobacco smoking and obesity and possible mechanisms for their combined effects, and for tailoring alcohol and tobacco policies and prevention strategies for obese people.

Chapter 9 Summary and future research

This chapter summarizes the results and contributions made by this thesis and provides recommendations for future work arising from this research.

9.1. Summary of the present work

The work presented in this thesis was designed to explore the relations between tobacco smoking and alcohol consumption and risk of CRC. A review of the literature revealed that there are various genetic and environmental factors, including tobacco smoking and alcohol consumption, which may have been associated with CRC risk, and may help explore substantial differences in the incidence of CRC among various subgroups by social and demographic characteristics and genetic characteristics. However, previous studies that explored the relations between tobacco and alcohol use and CRC have been inconclusive and inconsistent. One possible explanation is that previous studies that explored the impact of tobacco use and alcohol consumption on CRC risk have not adequately considered subgroup effects, and little research has reported on the combined effects of alcohol and tobacco and potential interactions with other risk factors.

The exploration of the relations between tobacco use and alcohol consumption and CRC risk, described in this thesis, was carried out using data from the population-based case-control study of CRC conducted in Newfoundland and Labrador of Canada.

The study also examined the extent of non-participation bias by analyzing some characteristics of eligible participants and non-participants. The reliability and validity of self-reported tobacco use and alcohol consumption in the case-control study were analyzed by comparing questionnaire response with the provincial data of tobacco and alcohol sales and the data from the Canadian Community Health Surveys. The major results and contributions of this thesis are summarized below.

9.1.1. Effect of cigarette smoking on colorectal cancer

This thesis found that cigarette smoking significantly increased the risk of CRC. There was 1.4 times increased risk of CRC among former smokers and 2 times increased risk of CRC among current smokers. The risk of CRC tended to increase significantly with greater cigarette smoking years, number of cigarettes smoked daily, and cigarette pack years. The risk tended to significantly increase when smoking cigarettes 20 years or longer or after starting smoking cigarettes 25 years.

This thesis also found that cigarette smoking produced a stronger effect on CRC risk among men, drinkers and male obese than women, non-drinkers and male and/or female non-obese. In male obese, for example, there were 2 times increased risk of CRC among former smokers and 3 times among current smokers compared to non-smokers.

The study found that cigarette smoking led to a significantly higher risk of rectal cancer than colon cancer. The risk of CRC slightly varied by survival status with a stronger effect among deceased than living CRC cases, by familial risk level with a stronger effect on CRC risk among cases with intermediate/high familial risk of cancer

than low familial risk, and by MSI with a stronger effect on MSI-H CRC risk than MSI-L/MSS CRC risk.

Furthermore, this thesis also found that the risk of CRC significantly decreased with greater number of years of abstention from smoking cigarettes. After abstaining from cigarette smoking 20 years or more, the risk did not differ from that for non-smokers. Among those subgroups which cigarette smoking produces a higher risk of CRC, the risk significantly decreased with years of abstaining from smoking cigarettes.

Given the inconsistence in existing literature around this issue, this thesis provides new and important evidence supporting the positive association between cigarette smoking and CRC. This adds to knowledge in the etiology of CRC. In addition to the observed stronger effects on CRC in men, and drinkers, this study found a stronger effect of cigarette smoking on CRC among male obese which have not been reported in previous studies. The thesis also revealed that the effects of cigarette smoking on CRC varied by CRC site, survival status of cases, familial risk level of cases and MSI status of cases.

9.1.2. Effect of alcohol consumption on colorectal cancer

The study first demonstrated a positive association between greater risk of CRC and higher lifetime alcohol intake in obese smokers, and a decreased risk of CRC among non-obese who never smoked in their lifetime. The results of this population-based case-control study conducted in NL demonstrated that the effect of alcohol intake on risk of developing CRC differed by weight status. Alcohol consumption tended to reduce the

risk of developing CRC among non-obese. The observed decreased effect did not vary substantially by subsite of CRC, survival status, familial risk level and MSI status. However, in the obese, the risk of CRC was 91% higher among alcohol drinkers than in non-drinkers. Drinkers who consumed three or more types of alcoholic beverage had 2.9 times greater risk of CRC relative to non-drinkers among the obese. The risk of developing CRC increased with the number of drinking years and the number of drinks daily among the obese. The effect of drinking on CRC risk was stronger among obese subjects who smoked. Drinking significantly reduced the risk of CRC among non-obese and weakened the effect of smoking on CRC among non-obese.

This thesis also found that alcohol consumption increased the risk of CRC for cases with low and intermediate or high familial risk among the obese, but a stronger effect for cases with intermediate or high familial risk; alcohol consumption increased the risk of CRC for cases with MSI-L/MSS and MSI-H among the obese, but a stronger effect for cases with MSI-H. These results suggest the combined effects of alcohol, body weight and gene mutation on CRC.

These results have implications for exploring the association between alcohol consumption and tobacco smoking and obesity and possible mechanisms for their combined effects on CRC risk. While there are no reports in the literature to investigate the joint effects of alcohol consumption, cigarette smoking and obesity on CRC risk, this thesis provides new and important evidence supporting the combined effects of alcohol drinking, smoking and obesity on CRC risk.

In the analyses, attempts were made to explore the potential impact of misreporting and non-participation bias. While it was concluded that these factors were unlikely to have had substantial impact on the results, it is possible that unknown confounders may have played a role. There are methodological weaknesses in many previous studies. Inadequate adjustment for various potential confounders (e.g. alcohol, physical activity, body size, dietary factors) or unidentified confounders could account for the small increase in risk found with smoking in some studies. For example, smokers are more likely than non-smokers to be physically inactive [454], to use alcohol, to have poorer dietary habits (e.g. lower consumption of fruits and vegetables and higher consumption of fat and meat) and they are less likely to be screened for CRC [277]. Each of these factors, in turn, is positively associated with CRC risk [117]. One of the strengths of this study was its attempt to control for the effects of all potential confounding variables. This design effectively controlled for intra-class correlations among census divisions within cells of the design since measures from within one geography may be highly correlated whereas those from different areas may be more likely to be independent of each other [382-384]. Therefore, the results presented in this thesis are highly valid.

9.2. Implications for health practice and change of individual lifestyle

The results of this thesis have important implications for public health practice and policy-making, and changes of individual smoking and drinking. Cigarette smoking is a notorious risk factor for cancer in organs such as lung, oropharynx, larynx and upper

digestive tract where there is direct contact with cigarette-related carcinogens [263]. This thesis found that cigarette smoking significantly increased CRC risk in NL. Over 13% of incidence of CRC can be attributed to cigarette smoking in the population. The combined effect of smoking with drinking and obesity can be significantly strengthened. People who have quit smoking are still at the elevated risk of CRC even many years later compared to non-smokers. Therefore, people should never start smoking and quit smoking in order to reduce the risk of CRC. Policy makers should incorporate quit smoking component into the existing prevention program of cancer.

There is convincing evidence that alcohol increases the risk of CRC in men and probably increases risk in women [41]. This thesis found that alcohol consumption significantly increased the risk of CRC among obese. Over 42% of incidence of CRC can be attributed to alcohol consumption among the obese. Drinking 20 years significantly increased the risk of CRC in obese. Obese who drink even 1-2 drinks per day had two times increased risk of CRC compared to obese non-drinkers. This combined effect of drinking with smoking can be strengthened among obese. While this thesis also found an reduced risk of CRC due to drinking when smoking and obesity are not present, the research suggests that non-obese who do not smoke drink in moderation and obese who smoke quit drinking and smoking and reduce their weight. Policy makers should initiate quitting drinking, smoking and obesity program to minimize the risk of CRC in NL.

9.3. Limitations of this thesis

The primary methodological concern has been the estimation of tobacco smoking, alcohol consumption and other risk factors. These exposures are difficult to estimate, given the complex nature of tobacco smoking and alcohol drinking behaviours and the limited ability of self-administered questionnaires to assess the use by study subjects several decades in the past. Although the assessments in this thesis suggested the impacts of tobacco smoking and alcohol consumption on CRC tended to be underestimated, further work is required to understand more about the effects of tobacco smoking and alcohol consumption on CRC risk. Given tobacco smoking through self-report approach in the case-control study has significantly been underestimated, the study instrument particularly about tobacco smoking is needed to be revised and validated.

An individual's body shape and size are represented by several measures including height, weight, body mass index, fat deposition patterns, and weight change. These measures are interrelated, but some of them such as fat deposition patterns are better predictors of CRC [16]. However, in the present study, only body mass index was calculated and the modified effect of obesity was examined based on this index. The true magnitude of the association between the exposures and CRC risk may not be estimated accurately.

Limitations of this thesis also include exposure misclassification regarding case-control status and inclusion of deceased cases and information collected from proxies of these deceased cases. Although the analyses were conducted to assess the extent of exposure misclassification, the true magnitude of the association could not be estimated accurately. This needs better procedures of data collection in the design stage. This study

included 258 deceased cases and their proxies were used. The response from proxies of these deceased cases might differ from those of living cases, possibly biasing the results. Thesis could not assess how other unknown confounders affected the observed association even though a recent review suggests that confounding is not important [422].

The participation rates of both cases and control subjects were relatively low and varied by case-control status (59.6% and 44.7%). It is possible that study respondents and non-respondents were different certain characteristics (e.g. smoking and drinking). This thesis was unable to accurately estimate the magnitude of the possible bias even though the analysis on the credibility of the data sources did not suggest any substantial effects.

9.4. Future research

9.4.1. Tobacco smoking and colorectal cancer

This thesis observed a significant association between cigarette smoking and CRC risk and the association varied by sex, alcohol drinking status, body weight, colon and rectum, survival status, familial risk level of cases and MSI status of cases. There has been a lack of consideration and/or inconsistent findings in previous studies of CRC etiology and epidemiology. Further studies are needed to investigate why the association between cigarette smoking and CRC varied by sex, drinking status and body weight. As well, more research is required to help clarify differences observed in the risk of colon and rectal cancer, living and deceased cases, and cases at different familial risk levels and MSI status of CRC cases with cigarette smoking.

Future research should consider the effect of exposure to environmental tobacco smoking on CRC risk when examining the effect of tobacco smoking on CRC risk. Previous studies on the incidence of CRC in relation to passive exposure to smoking observed a significantly increased risk of CRC for those exposed to environmental tobacco smoking [455,456]. The prospective cohort study conducted in the United States which investigated the incidence of CRC in relation to passive exposure to smoking observed an increased risk of CRC for non-smoking men exposed to secondhand smoking in the household (RR: 3.0 and 95% CI: 1.8-5.0) [455]. The Swedish population-based case-control study found an increased risk for colon cancer in women (OR: 1.8 and 95% CI: 1.2-2.8) and rectal cancer in men (OR: 1.9 and 95% CI: 1.0-3.6) in association with passive smoking after adjustment for numerous potential confounders [456]. It can be hypothesized a combined effect of smoking and exposure to environmental smoking on CRC risk. Future research should examine combined effects of tobacco smoking and exposure to environment tobacco smoking on CRC.

This thesis showed a significantly increased risk of CRC among non-obese smokers and obese male smokers, but a stronger effect of smoking was observed among obese men. No studies reported that there was a stronger effect of cigarette smoking on CRC by sex among obese than non-obese. Studies including this thesis observed that the association between smoking and CRC is stronger in men than in women [198,228,271]. Although it can be speculated that fewer cigarettes were smoked by women or more years of abstention from smoking and/or there may be hormone-related differences in susceptibility to smoking [41], future research is needed to investigate this sex difference.

Obesity is characterized by a low-grade chronic inflammatory state. Chronic inflammation can result in DNA damage and cancer promotion because a chronic inflammatory environment can increase proliferation and differentiation, inhibit apoptosis and induce angiogenesis [221]. Tobacco smoke is a major source of a wide variety of carcinogens including heterocyclic amines, polycyclic hydrocarbons and nitrosamines [333]. The combination of both smoking and obesity might result this stronger effect on CRC in obese. Future research need to further investigate this combined effect of smoking and obesity by sex.

This thesis found that smoking demonstrated a stronger effect on CRC among deceased than living CRC cases, and among cases of CRC with intermediate/high familial risk or MSI-H. The reason is unknown. This might be due to genetic cause of the difference observed in this study. Studies conducted in the United States showed that the higher frequency of the Pro/Pro phenotype of p53 in African American patients with colorectal adenocarcinoma is associated with an increased incidence of p53 mutations, with short survival [420]. More research is needed to clarify this.

9.4.2. Alcohol consumption and colorectal cancer

Previous studies have provided evidence that alcohol consumption may increase the risk of developing CRC [9,10,41,122,294,342,423,427], but this study found that drinking reduced the risk of CRC when smoking and obesity were not present, and increased the risk of CRC in the presence of smoking and obesity. Despite the fact that ethanol has been classified as a carcinogen [428], several studies on other types of cancers have

reported that alcohol intake reduced the risk of cancer [429-431,457]. This evidence suggests that alcohol may reduce the risk of cancer including CRC in which this thesis has found among non-obese who did not smoke. Further research is needed to examine this decreased effect and future research should also investigate why drinking alcohol lead to a reduced risk of CRC.

9.4.3. Methodological issues in future research

Future research must also consider several methodological issues in study designs. First is the study population. There is at least a 25-fold variation in occurrence of CRC worldwide [8,9]. The highest incidence rates are in North America, Australia and New Zealand, Western Europe, and, in men especially, Japan [8,9]. This international geographic variation in CRC risk can be explained by foods intake such as meat [13], fat [14], fibre [15] and lifestyle factors such as physical inactivity, excess body weight, and a central deposition of adiposity have major influences on risk of colon cancer [16]. There has been variation in CRC rates among provinces in Canada which had the highest incidence rates of CRC [10]. Incidence rates are obviously higher in eastern provinces than western provinces, for both men and women. However, the factors that cause these real differences are not well understood. It can be speculated that several factors including environmental factors, socioeconomic status, and genetic factors except alcohol consumption and cigarette smoking identified by this thesis may be associated with. Future research is needed to investigate whether cigarette smoking and alcohol consumption play key role in the development of CRC in Canadian population or

cigarette smoking and/or alcohol consumption combined with other risk factors increased the risk of CRC. Improved study designs in future research should consider this geographic variation factor.

Future research should use new and improved methods for assessing anthropometric factors to ensure standardized, reliable, and validated results. For example, abdominal fat may be a better indicator of the risk of CRC, but this measure was not included in this study. Studies should use all these anthropometric measurements.

More complete examination of confounding and effect modification by other risk factors should be done. Studies should investigate statistical interactions between tobacco, alcohol and other risk factors, particularly investigations of interactions with other molecular biological markers such as MSI. For example, the analysis in this thesis has suggested MSI-H might modify the impact of alcohol consumption on CRC, but the observation might be affected by the sample, i.e., small number of cases with MSI-H and future research should recruit more cases with MSI-H to determine this potential modified effect.

Research on drinking and smoking and weight control interventions, strategies and policies should be considered as the means for the primary prevention of CRC in NL. CRC prevention trials of reducing tobacco smoking and alcohol consumption interventions for CRC should be implemented at least among the obese who smoke and drink in Newfoundland and Labrador, given that evidence of this thesis has been provided by this thesis and evidence already exists to suggest abstaining from smoking

could reduce the risk of CRC and reducing the number of alcohol drinking could reduce the risk of CRC particularly among the obese.

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Appendices

Appendix I: The letter of ethics approval from the Memorial University Human Investigation Committee

MEMORIAL

Faculty of Medicine

[illegible]
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February 4, 2009

Reference #08.51

Mr. J. Zhao
C/o Dr. P. Wang
Division of Community Health
2nd Floor, Faculty of Medicine
Health Sciences Centre

Dear Dr. Zhao:

Thank you for your correspondence dated October 25, 2004, wherein you advise that the research study entitled **"Alcohol and tobacco use and colorectal cancer: A population-based case-control study in Newfoundland and Labrador"** is now complete.

Based on the information you have provided, please be advised we have officially closed the file pertaining to this research study.

Sincerely,

Fern Brunger, PhD
Co-Chair
Human Investigation Committee

John Harnett, MD, FRCPC
Co-Chair
Human Investigation Committee

RN;JH\jd

C Dr. C. Loomis, Vice-President (Research), MUN
Mr. Wayne Miller, Director of Planning & Research, HCCSJ
Meeting date: February 19, 2009

Appendix II: Epidemiological questionnaire in the Newfoundland familial colorectal cancer study

Newfoundland
Familial Colon Cancer Study

Personal History Questionnaire

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

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

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

Page 1

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

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

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 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

Page 3

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

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

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

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?

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

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
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

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

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

Page 7

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

22. Has a doctor ever told you that you had any 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

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

Medications

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

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

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 # 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, FiberCon. 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.

___ ___ 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

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

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
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

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

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

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
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

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

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

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

O yes
O no
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?

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

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 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

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

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

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

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

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46b. On average, when you ate red meat cooked by these methods, which of the following best describes its appearance?

What was its outside appearance?	What was its inside appearance? (how well done it was)?
O lightly browned	O red (rare)
O medium browned	O pink (medium)
O heavily browned or blackened	O brown (well-done)
O don't know	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

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

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

		For how many years?	During those years, for 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 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 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

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Alcohol Consumption

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

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

		For how many years?	During those years, how much did you typically consume?
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

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.

___ ___ number of alcoholic beverages a week
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.

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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.

___ ___ number of alcoholic beverages a week
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.

___ ___ number of alcoholic beverages a week
O never consumed alcohol

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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.)

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

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

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

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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

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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 $20,000 - $29,999
O $30,000 - $39,999
O $40,000 - $49,999
O $50,000 - $59,999
O $60,000 - $69,999
O $70,000 - $79,999
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 III: The letter of approval for databases from Wang

MEMORIAL UNIVERSITY

Faculty of Medicine
Division of Community Health and Humanities
The Health Sciences Centre
St. John's, NL Canada A1B 3V6
Tel: 709 777 6213/6652 Fax: 709 777 7382 www.med.mun.ca

January 31, 2008

Jinhui Zhao
206-1475 Pandora Avenue
Victoria BC
V8R 1A6

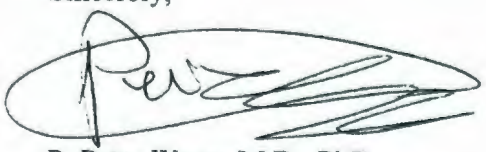
RE: **Request of epidemiological data of colorectal cancer in Newfoundland**

Dear Jinhui:

Thank you for your letter regarding the epidemiological data of colorectal cancer in Newfoundland population for your research entitled "Alcohol and tobacco use and colorectal cancer: a population-based case-control study in Newfoundland" in order for you to write your thesis as required by the PhD program in Community Health and Humanities at Memorial University of Newfoundland.

We have reviewed your request for the data files and will provide you the files requested for your research of alcohol and tobacco use and colorectal cancer. Thank you very much for the request.

Sincerely,



P. Peter Wang, M.D., PhD
Associate Professor of Epidemiology

PPW/sch

Appendix IV: Units of cigarettes sales and cigarette equivalents in Newfoundland and Labrador in 1980-2008

Year	Total Cigarettes Sold			Cigarettes Smoked among Population Aged 20-74 Years Old †		
	Units of Cigarettes (UC)	Cigarette Equivalents (CE)	Total units (TU)	Cigarettes (UCx0.9318)	Cigarette equivalents (UEx0.9318)	Total units (TUx0.9318)
1980	1,112,600	190,800	1,303,400	1,036,721	177,787	1,214,508
1981	1,089,800	205,500	1,295,300	1,015,476	191,485	1,206,961
1982	1,026,400	286,900	1,313,300	956,400	267,333	1,223,733
1983	738,600	432,300	1,170,900	688,227	402,817	1,091,045
1984	734,600	479,200	1,213,800	684,500	446,519	1,131,019
1985	771,500	493,400	1,264,900	718,884	459,750	1,178,634
1986	655,700	539,700	1,195,400	610,981	502,892	1,113,874
1987	*	*	*	*	*	*
1988	*	*	*	*	*	*
1989	694,956	412,166	1,107,122	647,560	384,056	1,031,616
1990	752,765	330,604	1,083,369	701,426	308,057	1,009,483
1991	630,842	304,398	935,240	587,819	283,638	871,457
1992	589,967	370,397	960,364	549,731	345,136	894,867
1993	476,882	285,384	762,266	444,359	265,921	710,279
1994	475,082	382,916	857,998	442,681	356,801	799,483
1995	446,391	397,250	843,641	415,947	370,158	786,105
1996	432,405	394,360	826,765	402,915	367,465	770,380
1997	418,343	388,784	807,127	389,812	362,269	752,081
1998	414,368	392,436	806,804	386,108	365,672	751,780
1999	430,729	382,214	812,943	401,353	356,147	757,500
2000	418,374	302,733	721,107	389,841	282,087	671,928
2001	427,879	259,210	687,089	398,698	241,532	640,230
2002	384,712	286,159	670,871	358,475	266,643	625,118
2003	354,939	292,687	647,626	330,733	272,726	603,458
Average	612,629	354,977	967,606	570,848	330,768	901,615

Source: Health Canada. Wholesales sales data: cigarette and fine-cut sales charts 1980-2008. Available at the website: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/indust/sales-ventes-eng.php (Accessed: September 17, 2009).

* Provincial sales not available for 1987 and 1988.

† Assumed 93.18% of absolute alcohol consumed by population aged 20-74 years old in CCHS 1.1 [357].

Appendix V: Total population and population aged 20-74 years old in Newfoundland and Labrador in 1971-2008

Year	Population and Smokers Aged 20-74			Cigarettes Smoked among Population Aged 20-74 Years Old †		
	Population (P)	Smoking Rate (R) †	Smokers (S=PxR)	Cigarettes in 1,000 (C) ‡	Cigarettes 1 Smoker (PS=C/S)	Packs Per Smoker (PP=PS/20)
1980	321,894	0.6659	214,346	1,214,508	5666.10	283.31
1981	328,048	0.6372	209,027	1,206,961	5774.20	288.71
1982	331,847	0.6097	202,331	1,223,733	6048.17	302.41
1983	340,079	0.5834	198,411	1,091,045	5498.91	274.95
1984	345,566	0.5583	192,920	1,131,019	5862.62	293.13
1985	349,836	0.5342	186,884	1,178,634	6306.76	315.34
1986	351,901	0.5112	179,883	1,113,874	6192.22	309.61
1987	355,742	0.4891	174,006	*	*	*
1988	359,670	0.4680	168,343	*	*	*
1989	364,504	0.4479	163,250	1,031,616	6319.22	315.96
1990	368,385	0.4286	157,876	1,009,483	6394.17	319.71
1991	374,321	0.4101	153,504	871,457	5677.11	283.86
1992	378,879	0.3924	148,674	894,867	6018.98	300.95
1993	382,720	0.3755	143,707	710,279	4942.56	247.13
1994	382,219	0.3593	137,331	799,483	5821.56	291.08
1995	380,155	0.3593	136,590	786,105	5755.23	287.76
1996	378,292	0.3296	124,685	770,380	6178.60	308.93
1997	375,328	0.3296	123,708	752,081	6079.48	303.97
1998	370,342	0.3125	115,732	751,780	6495.88	324.79
1999	368,385	0.3125	115,120	757,500	6580.07	329.00
2000	367,213	0.3183	116,884	671,928	5748.68	287.43
2001	365,140	0.3183	116,224	640,230	5508.58	275.43
2002	365,716	0.3048	111,457	625,118	5608.59	280.43
2003	367,759	0.2852	104,877	603,458	5753.98	287.70
Average	361,414	0.4309	153,990	901,615	5919.62	295.98

Source: The population data were obtained from Statistics Canada. The data are accessible: http://estat.statcan.gc.ca/cgi-win/CNSMCGI.EXE.
† Annual rate of smoker for 1980-2003 was estimated using the National Population Health Survey (NPHS) cycle 1, 2 and 3 [458-460] and CCHS 1.1 and 3.1 [357,360].
‡ Including cigarettes and fine-cut equivalents (see Appendix IV).

Appendix VI: Annual sales of alcoholic beverages by volume in Newfoundland and Labrador in 1992-2003

Year	Total Beverage in 1000 Litres				Total Absolute Alcohol in 1000 Litres †				Absolute Alcohol in 1000 Litres Consumed by Population Aged 20-74 Years Old ‡			
	Beer	Wine	Spirit	Total	Beer	Wine	Spirit	Total	Beer	Wine	Spirit	Total
1992	46,323	1,686	3,508	51,517	2,316	194	1,403	3,913	2,074	174	1,257	3,505
1993	46,048	1,622	3,344	51,014	2,302	187	1,338	3,827	2,062	167	1,198	3,427
1994	43,618	1,631	3,271	48,520	2,181	188	1,308	3,677	1,953	168	1,172	3,293
1995	42,060	1,629	3,225	46,914	2,103	187	1,290	3,580	1,883	168	1,155	3,207
1996	41,103	1,672	3,122	45,897	2,055	192	1,249	3,496	1,841	172	1,118	3,131
1997	39,307	1,746	3,108	44,161	1,965	201	1,243	3,409	1,760	180	1,113	3,053
1998	39,811	1,810	3,135	44,756	1,991	208	1,254	3,453	1,783	186	1,123	3,092
1999	41,538	2,069	3,221	46,828	2,077	238	1,288	3,603	1,860	213	1,154	3,227
2000	41,138	2,291	3,382	46,811	2,057	263	1,353	3,673	1,842	236	1,212	3,290
2001	42,210	2,492	3,148	47,850	2,111	287	1,259	3,656	1,890	257	1,128	3,275
2002	40,351	2,808	3,168	46,327	2,018	323	1,267	3,608	1,807	289	1,135	3,231
2003	43,257	2,160	4,543	49,960	2,163	248	1,817	4,228	1,937	222	1,627	3,787
Average	42,230	1,968	3,348	47,546	2,112	226	1,339	3,677	1,891	203	1,199	3,293

Source: Statistics Canada. Table 183-0006 - Sales of alcoholic beverages by volume, value and per capita 15 years and over, fiscal years ended March 31, annual (table), CANSIM (database), Using E-STAT (distributor). Ottawa. http://estat.statcan.gc.ca/cgi-win/CNSMCGI.EXE [355].

† Conversion factors for beer=5%; wine=11.5% and spirit=40% [346,355].

‡ Assumed 89.56% of absolute alcohol consumed by population aged 20-74 years old in CCHS 1.1 [357].

Appendix VII: Absolute alcohol consumption from beer, wine and spirits and per capita absolute alcohol consumption per drinker aged 20-74 years old in Newfoundland and Labrador in 1992-2003

Year	20-74 Years Old in NL			Absolute Alcohol in 1000 Litres				Per Capita Alcohol in Litres				% of Absolute Alcohol by Beverage			
	Pop	Rate †	Drinkers	Beer	Wine	Spirit	Total	Beer	Wine	Spirit	Total	Beer	Wine	Spirit	Total
1992	378,879	0.7661	290,259	2,074	174	1,257	3,505	7.15	0.60	4.33	12.07	59.19	4.95	35.86	100.00
1993	382,720	0.7661	293,202	2,062	167	1,198	3,427	7.03	0.57	4.09	11.69	60.17	4.87	34.96	100.00
1994	382,219	0.7661	292,818	1,953	168	1,172	3,293	6.67	0.57	4.00	11.25	59.31	5.10	35.58	100.00
1995	380,155	0.7661	291,237	1,883	168	1,155	3,207	6.47	0.58	3.97	11.01	58.74	5.23	36.03	100.00
1996	378,292	0.7677	290,415	1,841	172	1,118	3,131	6.34	0.59	3.85	10.78	58.78	5.50	35.72	100.00
1997	375,328	0.7677	288,139	1,760	180	1,113	3,053	6.11	0.62	3.86	10.60	57.65	5.89	36.46	100.00
1998	370,342	0.7818	289,533	1,783	186	1,123	3,092	6.16	0.64	3.88	10.68	57.65	6.03	36.32	100.00
1999	368,385	0.7818	288,003	1,860	213	1,154	3,227	6.46	0.74	4.01	11.20	57.64	6.60	35.76	100.00
2000	367,213	0.7835	287,711	1,842	236	1,212	3,290	6.40	0.82	4.21	11.43	56.00	7.17	36.83	100.00
2001	365,140	0.7852	286,708	1,890	257	1,128	3,275	6.59	0.90	3.93	11.42	57.72	7.84	34.44	100.00
2002	365,716	0.7906	289,127	1,807	289	1,135	3,231	6.25	1.00	3.93	11.18	55.92	8.95	35.13	100.00
2003	367,759	0.7958	292,657	1,937	222	1,627	3,787	6.62	0.76	5.56	12.94	51.15	5.87	42.98	100.00
Average	373,512	0.7765	289,984	1,891	203	1,199	3,293	6.52	0.70	4.13	11.35	57.42	6.16	36.42	100.00

Source: Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted) (table), CANSIM (database), Using E-STAT (distributor). Ottawa. http://estat.statcan.gc.ca/cgi-win/CNSMCGI.EXE (Accessed: September 17, 2009). The data of alcohol sales: see Appendix VI.

† Annual rate of drinker for 1992-2003 was estimated using the National Population Health Survey (NPHS) cycle 1, 2 and 3 [458-460] and CCHS 1.1 and 3.1 [357,360].