Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

[Randy Yu] Date

Associations of Serum Lipids with Risk of Incident, Sporadic Colorectal Adenoma]

By

Randy R. Yu
BS/BA

Department of Epidemiology

_____

Roberd M. Bostick, MD MPH
Committee Chair

Associations of Serum Lipids with Risk of Incident, Sporadic Colorectal Adenoma

By

Randy R. Yu

General Biology, Bachelor of Science/Psychology, Bachelor of Arts
University of California, San Diego
2008

Thesis Committee Chair: Roberd M. Bostick

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Department of Epidemiology
2011

Abstract

Title: Associations of Serum Lipids with Risk of Incident, Sporadic Colorectal Adenoma

Background: Colorectal cancer is the third most common cancer in the United States. There has been substantial evidence that environmental factors affect the risk of developing colorectal adenoma, precursors of colorectal cancer.

Objective: This study was conducted to investigate whether serum lipids are associated with risk of incident, sporadic colorectal adenomatous polyps.

Methods: Data were analyzed from a case-control study of incident, sporadic colorectal adenoma (n = 534) and colonoscopy negative controls (n = 644) conducted in Minnesota between 1990 and 1994. Self-administered questionnaires were used to collect demographic, dietary, and lifestyle information from all participants. Blood samples were drawn from participants to measure information on serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), and triglycerides. Multivariate logistic regression analyses were conducted to investigate the associations between serum lipid levels and risk of incident, sporadic colorectal adenoma.

Results: In the crude analyses, higher levels of HDL-C were associated with lower risk of colorectal adenoma (odds ratio (OR) = 0.57; 95% confidence interval (CI): 0.41, 0.80, highest quartile vs. lowest quartile), and higher levels of LDL-C were associated with higher risk (OR = 1.46; CI: 1.04-2.04, highest quartile vs. lowest quartile). Total cholesterol, VLDL-C, and triglycerides were not associated with risk of colorectal adenoma. In the multivariable analysis, higher levels of HDL-C were not associated with risk of colorectal adenoma (OR = 0.77; CI: 0.47-1.27, highest quartile vs. lowest quartile) and higher levels of LDL-C were not associated with risk of colorectal adenoma (OR = 1.05; CI: 0.68-1.61).

Discussions: Overall, serum lipid levels were not associated with risk for incident, sporadic colorectal adenoma. After adjustment for risk factors that tend to play a role in determining blood lipid levels, the associations of HDL-C and LDL-C were attenuated to close to the null value. These findings suggest that blood lipid levels may not affect risk for colorectal neoplasms; however, it is possible that exposures that influence HDL and LDL cholesterol levels may be more relevant to risk for the disease.

Associations of Serum Lipids with Risk of Incident, Sporadic Colorectal Adenoma

By

Randy R. Yu

General Biology, Bachelor of Science/Psychology, Bachelor of Arts
University of California, San Diego
2008

Thesis Committee Chair: Roberd M. Bostick

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Department of Epidemiology
2011

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my academic and thesis advisor, Dr. Roberd Bostick. Dr. Bostick has given me tremendous guidance and support through the process of data analysis and thesis writing. I want to thank him for giving me the freedom to explore on my own, and simultaneously giving me valuable advice and excellent teaching. I also want to thank Tom Ahearn for his guidance and support for the data analysis of this thesis. I have learned valuable knowledge from his sound guidance on data analysis.

I also want to thank my father and mother for their continued support throughout my academic career. My father's professional medical knowledge and more than 35 years of medical practice to bring better health for people in Taiwan has inspired me to pursue the field of public health and medicine. I would like to express my sincere gratitude to my uncle, aunt, and cousins for their moral support during my graduate study in Emory University. In addition, I want to thank Peiyin Hung for the constant source of encouragement and support throughout the road to finish this thesis. To them, I dedicate this thesis. .

Table of Contents

INTRODUCTION

We conducted a secondary data analyses to investigate the associations of higher levels of serum lipids and risk of incident, sporadic colorectal adenoma. This was a colonoscopy-based case-control study of incident, sporadic colorectal adenoma conducted by the Cancer Prevention Research Unit (CPRU), a collaboration of the University of Minnesota and Digestive Healthcare, a multi-site private gastroenterology clinic located in the metropolitan areas of Minneapolis, Minnesota.

As more countries are adopting western diets and lifestyles, hyperlipidemia and dyslipidemia have become important public health issues for chronic diseases [1-4]. The dietary factors and unhealthy lifestyle factors that are associated with colorectal cancer are also found to influence serum lipid levels unfavorably [5-9]. Thus, dyslipidemia, abnormal levels of serum lipid levels, could be consequences of these risk factors for colorectal cancer, rather than direct risk factors for colorectal carcinogenesis [10]. Serum lipid levels have been associated with neoplastic processes such as inflammation, oxidative stress, and insulin resistance [11-14]. Similarly, whether lipid serums are direct causal factors or correlated factors is inconclusive [10]. Previous studies that investigated the associations of higher serum lipids and risk of colorectal adenoma have shown inconsistent findings [15-28]. To our knowledge, data on associations between higher VLDL cholesterol levels and colorectal adenoma are scarce. We did not find higher levels of serum lipids to be associated with risk of incident, sporadic colorectal adenoma. In crude analyses, higher HDL and LDL cholesterol levels were statistically significantly associated with lower and higher risk of incident, sporadic colorectal adenoma, respectively. The significance of associations between higher HDL cholesterol

and LDL cholesterol levels in the crude analyses did not remain after multivariable adjustments. This suggests that higher levels of HDL and LDL cholesterol are not risk factors for colorectal adenoma, but are rather consequences of the covariates we adjusted for in the final model. In addition, there appears to be lower risk of colorectal adenoma among women and NSAID users above the first quartile of VLDL cholesterol levels. However, there was no dose-response association and no known biological plausibility, suggesting that these findings may be merely due to chance.

CHAPTER 1: BACKGROUND

Definition

The four sections of colon are ascending colon, transverse colon, descending colon, and sigmoidal colon [29]. The waste matter is led through the sigmoid colon and then goes through rectum before traveling out of the anus as feces [29].

Colorectal cancer is a cancer that originates from colon or rectum [29]. Colorectal carcinogenesis is a multi-year, multi-step process [29]. Colorectal cancer usually starts out with abnormal tissue growths in the wall of the colon [29]. The abnormal tissue growths usually begin as non-cancerous adenomatous polyps or hyperplastic polyps/inflammatory polyps [30]. Colorectal adenoma can be further characterized by their size, multiplicity, shape, histologic characteristics, and levels of dysplasia.

Descriptive Epidemiology

In 2010, colorectal cancer was the third most common cancer in both men and women in United States [31]. In 2010, an estimated of 102,900 new colon cancer cases and new 39,670 rectum cancer cases were expected in the United States [32]. Among the expected colon cancer cases in the United States, 49,470 colon cancer cases are expected among males and 53,430 colon cancer cases are expected among females [32]. Among the expected rectum cancer cases in the United States, 22,620 rectum cancer cases were expected among males and 17,050 rectum cancer cases are expected among females [32]. In 2010, a total of 51,370 colon cancer deaths were expected in 2010 [32]. Among the total number of colon cancer deaths estimated in 2010, 26,580 colon cancer deaths were expected among males and 24,790 among females [32]. The 2010 estimated numbers of

cases and deaths due to colon and rectal cancers are ranked third in both men and women [32]. Colon and rectal cancer cases comprise of 9% of the cancer cases among US males and 10% of the cancer cases among US females [32]. In addition, the estimated deaths due to colon and rectal cancer represented 9% of all cancer deaths among US men and women in 2010 [32]. Based on rates from 2005-2007 in Surveillance, Epidemiology, and End Results (SEER) registry, an estimated 5.12% of men and women born today will develop colon cancer or rectal cancer in their lifetime [33].

Among all races and ethnicities in the US, African Americans have the highest incidence rate of colorectal cancer [34-38]. African Americans also have a lower survival rates than Whites [39-46]. According to SEER registry data, the 2003-2007 colorectal cancer incidence rate was 68.1 per 100,000 among African American males and 55.4 per 100,000 among White males [32]. African Americans also had a higher colorectal cancer mortality rate than Whites [32]. From 2003-2007, the mortality rate among African American males was 30.5 per 100,000 and the mortality rate of White males was 20.6 per 100,000, suggesting higher mortality rates among whites [32]. The higher mortality rate from colorectal cancer can also be seen among African American females, with a mortality rate of 21.0 per 100,000 African American females as compared to the mortality rate of 14.4 per 100,000 White females [33].

Colorectal cancer is a common and deadly cancer in the United States. While colorectal cancer affects individuals in all races and ethnicities, the incidence and mortality rates among African Americans, both males and females, were higher than those of White males and females.

International Differences

Colorectal cancer has significant public health impact on all countries [47]. Globally, colorectal cancer ranks as the fourth most common cancer among men and third most common cancer among women [48]. The incidence of colorectal cancer is significantly different between westernized and developing countries [49]. According to the study by Center et al. (2009) using the most recent registry data from the International Agency for Research on Cancer (IARC), westernized countries have higher incidence rate than developing countries [50]. Colorectal cancer incidence rates have been increasing in less developed countries in Eastern Europe and South America [50]. The increase of colorectal cancer incidence in developing countries is correlated with the adoption of the western lifestyle, which often includes a high intake of meat, low intake of vegetables, lack of physical exercise, and alcohol drinking [3, 4]. Obesity, western dietary pattern, and sedentary lifestyle have been linked to increased colorectal cancer mortality [51].

Migration Studies

Epidemiologic studies of colorectal cancer among immigrants have significant potential in assessing colorectal cancer etiology, dietary risk factors, environmental risk factors, diagnosis, and treatment of colorectal cancer [1]. Migration studies are particularly useful when cancer incidence information is available for the source and host countries [52]. Singh et al., in a migration study using data from the National Vital Statistics System, found that the colorectal cancer mortality rate is lower among Asian immigrants than the non-immigrant US population [2]. Although lower than that of US-born non-Hispanic whites, the chronic disease incidence among US immigrants of

various racial and ethnic backgrounds increased with their duration of residence in the United States [2]. According to a systematic review conducted by Arnold et al., migrants from Asia, in particular from India, Ceylon, Bangladesh, and Indonesia have significant lower risk of developing colorectal cancer relative to the host population in six European countries [1]. In addition, Stirbu and colleagues, using cause of death and population registries in the Netherlands during 1995 -2000, found that age of migration is also an important factor for colorectal cancer mortality for non-western immigrants to the Netherlands [53]. They also found that non-western second generation migrants had lower colorectal cancer mortality than the native Dutch population, but higher colorectal mortality than first generation migrants [53]. The other findings by Stirbu et al. included that the younger the age of migration, the higher the colorectal cancer mortality [53]. Other studies found that the traditional diets which have less red meat and more vegetables of non-western immigrants in the Netherlands were inversely associated with colorectal cancer as they traditionally consume less red meat and more vegetables [54, 55]. These migration studies suggest that non-western migrants who are gradually abandoning their traditional diet and adapting to western dietary patterns increase their risk for colorectal cancer [53]. These studies suggest that western lifestyle and environmental factors play important roles in the etiology of colorectal cancer [56].

Colorectal Cancer Pathogenesis

The beginning phases of colorectal cancer carcinogenesis begin in disordered cell replication in the normal colonic mucosa and the growth of clusters of aberrant crypts with abnormal proliferation [57]. The disordered cell replication leads to the formation of adenomatous polyps which are masses of dysplastic epithelia with uncontrolled crypt cell

division [57]. Most colorectal malignancies arise through malignant mutation of benign adenoma in the process of the adenoma-to-adenocarcinoma sequence [57, 58]. Advanced colonic lesions adenomas are large (≥1.0 cm), villous histology, and high-grade dysplasia [59].

The adenoma-adenocarcinoma sequence involves mutations of several oncogenes and tumor suppressor genes [60]. The mutation of the adenomatous polyposis coli gene, a tumor suppressor gene, initiates the adenoma-adenocarcinoma sequence by stimulating the growth of small adenoma from a normal mucosa [61]. The adenomatous polyposis coli gene regulates the cell cycle progression, differentiation, apoptosis, and migration of the colonic epithelial cell [62]. Mutations in the Adenomatous Polyposis Coli gene (APC) were found to be present in over 80% of colorectal adenomas and colorectal carcinomas while the gene has been characterized as one of the earliest mutations in the colon cancer carcinogenesis [62]. In addition, the well-known syndrome, familial adenomatous polyposis, which results in thousands of colorectal adenomas, is due to autosomal dominant inheritance of the mutated APC gene on chromosome 5q21 [63].

Mutations in the K-ras oncogene are common in colon cancer carcinogenesis [64]. Many cases of colorectal cancer have K-ras mutations that jointly mutate K-ras isoforms of K-ras 4A and K-ras 4B [65]. K-ras oncogene mutations were found to be present in over 40 percent of colorectal adenomas and cancers [64]. The mutations of the K-ras oncogenes appear to stimulate early colorectal adenoma to further grow into larger and more advanced adenoma [66]. K-ras mutations give selective growth advantage for early adenoma to increase their size for potential transformation into carcinoma [66]. Barry et al, found a low rate of K-ras mutation among smaller and earlier colorectal adenomas but

a higher rate among larger and more histologically advanced colorectal adenomas [67]. In addition, Boughdady et al, found the rate of K-ras mutations increased with adenoma size and dysplasia severity [66].

Mutations in the DCC ("Deleted in Colorectal Cancer") gene, a tumor-suppressor gene on chromosome 18, also have a role in the adenoma-carcinoma sequence [68]. The DCC gene has important cellular functions such as mediating cell growth and differentiation [68]. Loss of this gene may interfere with these cellular functions and may play a role in colorectal pathogenesis [68]. The mutations in the DCC gene also have been associated with the progression of early colorectal adenoma to late adenoma [69]. Vogelstein, in a study conducted in the 1990's, found that the DCC gene was deleted in more than 70% of colorectal cancers [70]. In addition, loss of DCC protein expression, along with loss of heterozygosity (LOH) of chromosome 18q, was associated with more advanced colorectal adenoma [71].

The p53 gene mutation is a late genetic event in the progression from colorectal adenoma to colorectal carcinoma [72]. The p53 regulates the DNA repair process and is also required for cell apoptosis in response to DNA damage [73]. In colorectal cancer pathogenesis, the genetic mutations occur in the region of exons 5 to 8, and the structural domains of the p53 gene [72]. Giaretti et al, in an intra-tumor comparative analysis of the K-ras oncogene and p53 gene, have found p53 mutations to be significantly associated with colorectal adenoma with early cancerous cells with severe dysplasia (p-value = 0.01) [74]. The loss of p53 functions results in genomic instability is the final genetic change in the transformation of adenoma to carcinoma [73]. In addition, approximately 5% of colorectal cancer is due to autosomal dominant inherited mutations [75]. Familial

Adenomatous Polyposis (FAP) is due to a mutation in the APC gene, and causes approximately 1-2% of colon cancers. The most common form of hereditary colorectal cancer is the hereditary non-polyposis colorectal cancer syndrome, or Lynch Syndrome [75]. The cause of the syndrome is primarily due to heterozygous germline mutations in one of the mismatch repair genes of hMLH1, hMSH2, hMSH6, and hPMS2. [75] The heterozygous germline mutations results in mismatch repair deficiency that leads to the growth of numerous tumors in the colon [75].

Obesity and Body Size

Body Mass Index

Researchers have suggested that body mass index (BMI) influences the hormones in the insulin growth factors/growth hormone axis [76]. Obesity is associated with elevated levels of insulin growth factor and growth hormones, which has been known to stimulate cell proliferation and inhibit cell apoptosis [77-79].

Previous studies of adenoma have consistently found direct associations of obesity with colorectal adenoma. In a colonoscopy-based case-control study, Stein et al. found obesity (BMI$\geq$30 kg/m^2) to be significantly directly associated with advanced neoplasia (Odds ratio (OR) = 3.83; 95% CI (CI): 1.94-7.55) [80, 81]. In another case-control study (n = 2,465 subjects with colorectal adenomas), found obesity to be directly associated with colorectal adenoma recurrence over a follow-up of 3.1 years among subjects with family history of colorectal cancer [81].

These consistent findings suggest obesity is strong risk factor for colorectal adenoma. Obesity relates to numerous factors such as unhealthy dietary patterns and lifestyle habits.

Waist-to-hip ratio

Waist-to-hip ratio (WHR) is an anthropometric factor that is indicative of central adiposity [82]. Central adiposity is one of the consequences from high-fat diet and insufficient metabolic expenditure [83]. Numerous epidemiological studies have investigated the associations of WHR and colorectal adenoma [84]. In a prospective cohort study, Giovannuci et al. found higher waist-to-hip ratios are associated with higher risk of colorectal adenoma (Relative risk (RR) = 3.41; Cl: 1.52-7.66; P_{trend}: 0.01) [84]. In another study, Lee et al. found higher waist-to-hip ratios to be associated with higher risk of colorectal adenoma (OR = 10.13; CI: 2.00, 51.17) [85].

In addition to obesity, central adiposity, as indicated by high waist-to-hip ratio, is also a strong anthropometric risk factor for colorectal adenoma and cancer [86].

Dietary Factors

Since colorectal cancer pathogenesis is a long multi-step process, there may be multiple opportunities for dietary factors to influence the risk of colorectal cancer. In a comprehensive population-based case-control study of colorectal cancer in Melbourne Colorectal Cancer Study, over 46% of patients with colorectal cancer have five or more dietary risk factors [87]. Numerous studies have supported the hypothesis that western diet, a diet characterized by high intake of calories, animal fats and meat, and refined carbohydrates and low consumptions of fibers, vegetables, and fruits, as high risk factors for colorectal cancer [88].

Animal Fat and Meat

Numerous epidemiologic studies have supported the hypothesis that high intakes of meat, animal fat, and animal proteins are positively associated with colorectal cancer

[89]. High-fat diet promotes the development of colorectal cancer by increasing the excretion of bile acids which digests fat by emulsifying fat molecules for nutrient absorption in the small intestine [90, 91]. One important effect of high bile acid exposure is the formations of reactive oxygen species (ROS) and reactive nitrogen species (RNS) on the colonic cells [91]. Increased formations of ROS and RNS may lead to increased DNA damage and eventually leads to increased DNA mutations that lead to colorectal neoplasia [91]. Although repeated exposure of colonic cells to high concentrations of bile acids appears to be a major etiologic factor for colorectal carcinogenesis, high intake of heme iron is also a significant risk factor, as iron has a role in catalyzing formations of ROS [92].

In addition, high intake of high-fat and high-beef products results in significantly higher excretion of fecal secondary bile acids of deoxycholic acid (DCA) and lithocholic acid (LCA) [93]. It has been found that the most significant bile acids in the colorectal carcinogenesis are DCA and LCA [94]. Excessive exposure of colonic cells to DCA results in mutations of mitosis-related and chromosomal maintenance genes [95]. Excessive bile acids and nicotine from smoking may also interact synergistically in colonic cells to further increase the DNA damage and oxidative stress that may eventually leads to colorectal carcinogenesis [96].

In a meta-analysis conducted by Larsson et al., 15 prospective studies on meat intake (n = 7,367 colorectal cancer cases) and 14 prospective studies (n = 7,903 colorectal cancer cases) found high intake of red meat was associated with higher risk of colorectal cancer (RR = 1.28; Cl: 1.15, 1.42) [87]. High consumption of processed meat was also found to be associated with higher risk of colorectal cancer (RR = 1.20; Cl: 1.11,

1.31) [87]. Larsson et al. also found a daily dietary intake increase of 120 grams (g)/day of red meat and 30 g/day of processed meat had a 28% and a 9% higher risk of colorectal adenoma, respectively.

Another hypothesis for meat consumption increasing the risk of colorectal cancer relates to the methods of meat preparation methods [97, 98]. Polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) are mutagenic compounds that are formed when meat products are fried under high temperatures and cooked well-done [99-101]. Several epidemiological studies have investigated associations between levels of heterocyclic amines and colorectal adenoma. In a large prospective European cohort study, Rohrmann et al. found higher levels of 2-amino-1-methyl-6 phenylimidazol[4,5-*b*] pyridine (PhIP) are associated with higher risk of colorectal adenoma (RR =1.47; CI: 1.13, 1.93) [102]. In a cross-sectional study, Ferrucci et al. also found higher levels of heterocyclic amines (2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline), relative to low levels of the heterocyclic amines, are associated with higher risk of colorectal adenoma (OR = 1.90; Cl: 1.05, 3.42) [97].

Consistent findings suggest that high fat intake and high meat consumptions are strong risk factors for colorectal adenoma and cancer. High meat consumptions can lead to excessive excretions of bile acids, which can lead to mutations in the colonic cells. Meat preparation methods are also important in the colorectal cancer carcinogenesis, as over-frying of meat could lead to formations of mutagenic compounds of heterocyclic amines and polycyclic aromatic hydrocarbons.

Dietary Fiber

Fiber consumptions have been hypothesized to be inversely associated with risk of colorectal cancer [103]. One direct biological mechanism is that fiber can absorb carcinogens and lower the exposure of the colonic mucosal cells to these substances [103]. Another biological mechanism is high amount of fiber in the colon shortens the stool transit time [103]. In addition, butyrate, a product of fiber degradation by bacterial enzymes, reduces the activity of tumor promoters in the colon [103].

For the past three decades, epidemiological studies have investigated the association between colorectal adenoma and dietary fiber intake, but results have been inconclusive [104]. Asano et al. conducted a systematic review and meta-analysis of five randomized clinical trials (N = 4,349 participants) to assess the effect of dietary fiber on incidence and recurrence of adenoma [103]. Asano et al. did not find any evidence that high intake of fiber will reduce the incidence or recurrence of colorectal adenoma within two to four year period [103]. However, several studies did found inverse associations between intakes of dietary fiber and colorectal adenoma. In a case-control study (n = 3,057 cases, n = 29.413 controls), Millen et al. found higher intake of fruit (5.7 pyramid servings/day), relative to lower intake (1.2 pyramid serving/day), were associated with lower risk of colorectal adenoma [105]. However, Millen et al. did not find higher levels of vegetable intake, as compared to lower level, to be associated with risk of colorectal adenoma [105].

Despite the inconsistent results of these studies suggest the inconclusiveness of dietary fiber and colorectal adenoma, several plausible biological mechanisms of actions

for dietary fiber in the carcinogenesis have been proposed [105]. Further studies should be conducted to investigate the associations between dietary fiber and colorectal cancer.

Calcium

Higher levels of dietary calcium have been hypothesized to be associated with lower risk of colorectal adenoma [106, 107]. Colonic luminal calcium binding to calcium receptor may directly modulate the cell cycle of colonocytes by lowering the concentration of 25-hydroxyvitamin D 24-hydroxylase [107], promoting activation of E-cadherin [108], and inhibiting the β-catenin/T-cell factor transcription complex [108, 109]. Luminal calcium has been hypothesized to bind secondary bile acids and ionized fatty acids [108, 110].

In a systematic review and a meta-analysis of six randomized clinical trials, Carroll et al. found supplemental 1200 to 2000 milligram/day significantly reduced the risk of adenoma recurrence by 20 percent among individuals with a history of colorectal adenomas [106]. Carroll et al. did not find dietary and supplementary calcium to have an effect on number of colorectal adenoma among individuals with familial adenomatous polyposis. In addition, in meta-analysis of two clinical trials, Carroll et al. did not find dietary and supplemental calcium, with or without vitamin D, to have an effect on the relative risk of colorectal cancer [106].

Clinical trials have indicated that supplemental calcium has an effect in reducing the adenoma recurrence among individuals with history of colorectal adenoma. The evidence from these studies has supported the biological mechanisms that high levels of calcium have a role in the colorectal cancer carcinogenesis.

Vitamin D

Higher levels of vitamin D have been hypothesized to be associated with lower risk of colorectal adenoma. Vitamin D has a role in facilitating the metabolism of calcium [111]. In addition, vitamin D may inhibit cell proliferation and promote cell differentiation and cell apoptosis [112, 113].

The 25-hydroxyvitamin D, the precursor to the active metabolite 1α, 25-Dihydroxyvitamin, results from vitamin D dietary intake and skin exposure to sunlight [113]. The enzyme 1α-hydroxylase and vitamin D receptors that convert 25-hydroxyvitamin D to 1α, 25-Dihydroxyvitamin has been recently found to be expressed in the colonic tissues [114, 115].

Epidemiologic studies have indicated higher levels of vitamin D are associated with lower risk of colorectal cancer [113]. In a systematic review of observational studies of serum 25-hydroxyl-vitamin level and colorectal adenoma (N = 2,630 participants), Gandini et al., found higher levels of 25-hydroxyvitamin D are associated with lower risk of colorectal cancer [113]. Gandini et al. also found a 10 ng/ml increase of serum 25-hydroxyvitamin D to be associated with lower risk of colorectal cancer. (Summary relative risk = 0.85; 95% CI: 0.79-0.91) [113].

Studies also have shown higher levels of serum 25-hydroxyvitamin D levels are associated with lower risk of colorectal adenoma. [116] In a meta-analysis of 17 studies, Wei et al. found that higher levels of 25-hydroxyvitamin D, as relative to lower levels of 25-hydroxyvitamin D, is significantly statistically associated with lower risk of colorectal adenoma (OR = 0.70; CI: 0.56-0.87) [116]. Wei et al. also found participants in the highest quintile of 25-hydroxyvitamin D to have a 36 percent lower risk for advanced

colorectal adenoma than those in the lowest quintile of 25-hydroxyvitamin D [116].

Studies that examined vitamin D using serum 25-hydroxyvitamin D, the best indicator for vitamin D, have consistently found higher levels of vitamin D are associated with lower risk of colorectal cancer.

Other Lifestyle Factors

Physical Activity

Physical activity has been consistently inversely associated with risk for colorectal cancer [117]. Physical activity may reduce risk of colorectal cancer by several mechanisms which include: enhancing the immune system, increasing gut motility, decreasing obesity, decreasing insulin and insulin-like growth factor levels, and influencing prostaglandin levels [118].

In a prospective cohort study of 488,720 participants of ages 50-71, Howard et al. found men who regularly exercised five times a week had lower risk of colon cancer, compared to men who rarely or never exercised on a weekly basis (RR = 0.79; Cl: 0.68, 0.91; P_{trend} = 0.001) [119]. In a case-control study of 177 adenoma cases and 228 controls identified in North Carolina from 1995-1997, subjects with higher physical activity level plus a low waist-to-hip ratio were at substantially lower risk for incident, sporadic colorectal adenoma (OR = 0.32; CI: 0.16, 0.62) [120].

Higher levels of physical activity have found to have consistent inverse associations with colon cancer [121]. Although the findings on physical activity and colorectal adenoma are more limited, the biological mechanisms of the role of physical activity and colorectal adenoma remain significant in colorectal carcinogenesis [121].

Alcohol Consumption

Numerous studies suggested that alcohol consumption that alcohol consumption is also a risk factor for colorectal adenoma. Huxley et al., in a systematic review and meta-analysis (15 cohort studies; N = 13,657 individuals with colorectal cancer), found high alcohol consumption, relative to light drinking and no drinking, was associated with higher risk of colorectal cancer [122]. Hermann et al. conducted a prospective study of 25,540 subjects recruited in Germany during 1994-1998 to investigate the association of alcohol consumption with risk of colorectal adenoma [123]. A total of 536 cases of colorectal adenoma were identified by 2007, and subjects with the highest alcohol consumption (≥30 g/day) had a significantly lower risk for colorectal adenoma compared to those with the lowest consumption (≤5 g/day) (OR = 1.63; CI: 1.21-2.22) [123]. In another hospital-based cross-sectional study of 4,413 Taiwanese (n = 654 cases; n = 3,769 controls), Liao et al. found habitual alcohol drinking to be significantly directly associated with rectosigmoid adenoma among male subjects [124].

Findings from past epidemiological studies suggest consistent results that suggest higher levels of alcohol consumptions are associated with higher risk of colorectal adenoma and cancer.

Smoking

Cigarette smoking has also been found in epidemiological studies to be risk factor for colorectal neoplasia [125]. Carcinogens from cigarette smoke may cause irreversible genetic damage in the normal colorectal mucosa [126]. Excessive bile acids and nicotine from smoking may also interact synergistically in colonic cells to further increase the DNA damage and oxidative stress that may eventually leads to colorectal carcinogenesis.

[96]

Since smoking has been hypothesized to have a role in colon cancer carcinogenesis, numerous studies have examined this relationship. Giovannucci et al., in a systematic review, found individuals who smoke one to two packs per day or 20-40 cigarette pack-years have two to five-fold higher risk of colorectal adenoma than non-smokers [126]. In a case-control study of tobacco use among 4,383 cases with colorectal adenoma or hyperplastic polyps and 33,667 controls with no confirmed polyps, current smoking was directly associated with colorectal adenoma (OR = 1.8; CI: 1.50-2.10) [127]. In another case-control study with 2,707 subjects who had undergone colonoscopy in 2009, Anderson et al. found that having smoked over 30 pack-years was associated with higher risk of colorectal adenoma (OR = 2.40; 95% CI: 1.65-3.50) [125]. Findings have been consistent on associations of cigarette smoking and risk of colorectal adenoma.

Medication Use

Hormone Replacement Therapy

Studies found hormone replacement therapy (HRT) to be inversely associated with colorectal carcinogenesis and adenoma among women [128]. Several biological mechanisms by which HRT is involved in reducing the risk of colorectal cancer have been proposed [129]. There are several hypotheses as to how hormone replacement therapy affects pathways leading to colorectal carcinogenesis. It is hypothesized that hormone replacement therapy decreases the production of secondary bile acids which can trigger mutations in the colonic cells [91, 130]. In addition, hormone replacement therapy has been proposed to decrease the production of insulin-like growth factor 1 (IGF-1) which is associated with risk of colorectal adenoma [130-133].

In a review and meta-analysis, Grodstein et al. investigated the association of postmenopausal hormone therapy and the risk of colorectal cancer. In the meta-analysis, 18 epidemiological studies including one clinical trial, nine prospective cohort studies, and eight case-control studies have been examined [134]. The result suggests current use of hormone therapy users, as compared to no use of hormone replacement therapy was associated with lower risk of colorectal cancer (RR = 0.66; Cl: 0.59, 0.74) [134]. In a case-control study, Terry et al. found that ever use of hormone replacement therapy was significantly inversely associated with risk of advanced colorectal adenoma among women (OR = 0.40; CI: 0.20-0.90) [135]. In another colonoscopy-based case-control study of 755 women aged 56 or older (adenoma cases= 169, colonoscopy-negative controls=586), current use of hormone therapy replacement was significantly associated with lower risk for colorectal adenoma (OR = 0.40; CI: 0.16-0.98; *p*-trend = 0.03) [136]. These findings suggest that hormone replacement therapy is associated with lower risk of colorectal adenoma.

Non-Steroidal Anti-Inflammatory Drugs/Aspirin

Inflammation has been known as a critical factor in the development of colorectal cancer [137]. Both intrinsic inflammation (via inflammatory cells and mediators within the tumor) and extrinsic inflammation related to chronic inflammatory conditions contribute to tumor progression [138]. Pro-inflammatory conditions, such as the inflammatory bowel disease, increase the risk of colorectal cancer [139]. Although colorectal cancer does not always develop after histories of inflammatory bowel disease, inflammation is a critical factor in the development of colorectal cancer [139].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been hypothesized to

lower the risk of colorectal cancer by inhibiting the cyclooxygenase enzymes [137, 140]. NSAIDs inhibit the cyclooxygenase enzymes (COX-1 and COX-2 enzymes) [137]. The COX-2 enzymes are involved in the synthesis of prostaglandins and prostacyclins from arachidonic acid [139]. It has been found that COX-2 is over-expressed in approximately 40 percent of colorectal adenomas and 80 percent of adenocarcinomas [141]. In addition, numerous studies have indicated that aspirin has anti-neoplastic effect that affects the colorectal carcinogenesis [142].

In a systematic review, Rostom et al. investigated whether NSAIDs and Cyclooxygenase-2 inhibitors were associated with lower risk of colorectal adenoma. In one cohort study compiled in the review, any use of NSAIDs for four years, as compared to no use of NSAIDs, was found to be associated with lower risk of colorectal adenoma among participants with previous history of colorectal adenoma (RR = 0.64; CI: 0.48, 0.85) [143]. According to eight case-control studies compiled by the review, the pooled estimate indicates that participants who regularly used non-aspirin NSAIDs have a 46 percent lower risk of colorectal adenoma than those who reported to not use non-aspirin NSAIDs. In a meta-analysis of four clinical trials, with a total of 2,967 randomized subjects, aspirin in doses ranging from 81 to 325 mg/day was found to reduce the risk of colorectal adenoma (RR = 0.83; CI: 0.72-0.96) [142].

Coupled with the proposed biological mechanisms and plausibility, these findings provide evidence that regular use of NSAIDs and aspirin may reduce the incidence of colorectal adenoma.

Hyperlipidemia/Dyslipidemia

In countries with a high incidence of colorectal cancer, obesity, high fat diet,

alcohol consumption, smoking, and low levels of physical activity are associated with increased risk of colorectal cancer [144-147]. These factors are also associated with hyperlipidemia [148]. The dietary factors and unhealthy lifestyle factors that are associated with colorectal cancer are also found to influence serum lipid levels unfavorably [5-9]. Thus, dyslipidemia, abnormal levels of serum lipid levels, could be consequences of these risk factors of colorectal cancer, rather than direct risk factors for colorectal carcinogenesis [10]. Serum lipid levels have been associated with neoplastic processes such as inflammation, oxidative stress, and insulin resistance [11-14]. Similarly, whether lipid serums are direct causal factors or correlated factors for the neoplastic processes is inconclusive [10].

Total Cholesterol

Hypercholesterolemia often causes sclerotic changes in blood vessels, hypoxia in large intestine tissues, and homeostasis changes in the intestine tissues [149, 150]. The genetic and molecular changes in the normal colonic epithelial cells lead to the growth of colorectal adenomatous polyps, which are the precursors to colorectal cancer [149, 150].

Cholesterol catabolism is linked with the biosynthesis of bile acids, which are physiologically agents required for disposal of cholesterol, fats, and vitamins [109]. However, excessive bile acids are mutagenic, and excessive amount induces oxygen and reactive nitrogen species, and select for apoptosis resistance in the colonic mucosa [91]. Cholesterol catabolism to primary bile acids can be initiated by two pathways: a classic pathway via 7-alpha-hydroxylase, and an acidic pathway via mitochondrial sterol 27-hydroxylase [151].

Results from epidemiological studies on association between cholesterol level and

colorectal adenoma have not been consistent. Chung et al., in a case-control study (n=105 histologically confirmed patients and 105 age, sex-matched controls with normal colonoscopy results), found that relative to those in the lowest tertile of cholesterol level (below 179 mg/dl), those with a cholesterol level ≥ 210 mg/dl were not at higher risk for colorectal adenoma. (OR = 0.7; CI: 0.3-1.4) [15]. In another case-control study (n = 476 sigmoidoscopy-confirmed adenoma cases, n=520 sigmoidosocopy-negative controls), there was no association of total cholesterol with adenomas in the left colon and rectum [23]. In a case-control study (n = 88 colonoscopy-confirmed cases, n = 1,055 colonoscopy-negative controls) of Japanese self-defense officials in Japan, cholesterol was not associated with colorectal adenoma [16]. Kamiya et al., in another small case-control study (N = 283), a cholesterol level of ≥ 209 mg/dl, relative to a reference level of < 181 mg/dl, was positively associated with colorectal adenoma among subjects in 40-49 years old (OR = 13.75; CI: 2.32-81.49), but not among those in other age groups [17]. Several studies did not adjust for important lipid confounders such as total energy (kcal), saturated fat, and monounsaturated fat, and polyunsaturated fat. Only the study conducted by Bird et al., have adjusted for total energy and saturated fat [23]. The results of observational epidemiologic studies of cholesterol level and colorectal adenoma have been inconsistent and further studies are needed to clarify whether or not there is an association.

High-Density Lipoprotein Cholesterol

High-density lipoprotein cholesterol is a predictive marker of cardiovascular disease as a high level of the HDL is associated with lower risk of atherosclerosis, myocardial infarction, stroke, and other cardiovascular events [152]. The protective

effect of HDL on cardiovascular disease is attributed to its ability to drive reverse cholesterol transport [152].

Low levels of HDL are very common among individuals who are adapting to western diets and sedentary lifestyles. The undesirable low levels of HDL are common among obese individuals who consume high amounts of saturated fat and alcohol [153]. Many of the determinants of HDL levels are also considered risk factors for colorectal cancer [154, 155].

Few epidemiological studies have been conducted to investigate associations between HDL and colorectal adenoma, and the results of these studies are not consistent. A hospital-based case-control study (n = 194 cases, n = 628 colonoscopy-negative controls), Bayordoffer et al. found HDL cholesterol levels to be inversely associated with the frequency of colorectal adenomas among male and female cases (OR = 0.36; CI: 0.21-0.62) [18]. In a case-control study (n = 476 sigmoidoscopy-confirmed adenoma cases, n = 520 sigmoidosocopy-negative controls), Bird et al. found higher levels of HDL were not associated with colorectal adenoma in the left colon and rectum (OR=1.1; CI: 0.7-1.6) [23]. In another case-control study (N = 2,389), Liu et al. investigated associations between components of metabolic syndrome and colorectal adenoma. Low HDL levels were found to be positively associated with risk of colorectal adenoma (OR = 1.30; CI: 1.10-1.54) [20]. These studies also did not adjust for important lipid confounders such as total energy (kcal), saturated fat, monounsaturated fat, and polyunsaturated fat. Further studies are needed to clarify whether HDL is associated with lower risk of colorectal adenoma.

Low-Density Lipoprotein Cholesterol

Cardiovascular diseases are strongly associated with elevated low-density lipoprotein cholesterol [156]. Vegetarian diets have been linked to lower LDL cholesterol levels, lower prevalence of obesity, and reduced risk of chronic diseases such as diabetes mellitus and hypertension [157].

To date, there are few published studies on an association between LDL cholesterol levels and colorectal adenoma. The results of these studies have been inconsistent. Bayordoffer et al., in a case-control study (n = 194 cases, n = 628 colonoscopy-negative controls), have found that high LDL cholesterol levels to be positively associated with colorectal adenoma (OR = 2.31; CI: 1.36-3.92) [18]. Park et al., in a case-control study (n=134 cases, n=134 colonoscopy-negative controls), have found increasing LDL cholesterol levels to be associated with increasing risk of colorectal adenoma, but the findings were not statistically significant [21]. Further studies on LDL cholesterol levels and colorectal adenoma are needed to clarify whether or not they are associated.

Very-Low-Density Lipoprotein Cholesterol

To date, there are few published on an association of VLDL cholesterol levels with colorectal adenoma. In the above described study conducted by Bayordorffer et al., high VLDL cholesterols level were directly associated with frequency of colorectal adenoma (OR = 1.72; CI:1.30-2.86) [18]. Further studies on VLDL cholesterol levels and colorectal adenoma are needed to clarify whether or not they are associated.

Triglycerides

A hypothesized has been proposed that that factors associated with higher risk for

colorectal cancer, such as obesity, Western diet, and alcohol consumption are also associated with higher serum triglycerides, while factors associated with lower risk of colorectal cancer, such as physical activity and fiber intake, are also associated with lower serum levels of triglycerides [155].

High levels of triglyceride have been associated with colorectal adenoma. In a case-control study of 782 colorectal adenoma cases and 738 controls in Japan, Otani et al. found that those in the highest quartile of triglyceride levels, relative to those in lowest quartile, were at higher risk for colorectal adenoma (OR = 1.5; CI: 1.1-2.0), and even more so for having three or more colorectal adenoma(OR = 2.3; CI: 1.3-4.2) [22]. Park et al. in a case-control study of 134 confirmed colorectal adenoma cases and 134 controls, found a statistically significant trend of increasing colorectal adenoma risk with increasing triglyceride levels (P-trend = 0.01) [21].

Conclusion

Prior published studies generally focused only on total cholesterol level in investigating the association between blood lipids and colorectal adenoma. There have been relatively few, mostly small case-control studies with various limitations. Several studies did not adjust for important lipid confounders such as total energy (kcal), saturated fat, and monounsaturated fat, and polyunsaturated fat [15, 21, 23, 27, 158].

Also, prior studies did not investigate associations between blood lipids and adenoma characteristics such as size, multiplicity, shape, histologic characteristics, and levels of dysplasia [15, 21, 23, 27, 158].

CHAPTER 2: MANUSCRIPT CHAPTER

Abstract

Title: Associations of Serum Lipids with Risk of Incident, Sporadic Colorectal Adenoma

Background: Colorectal cancer is the third most common cancer in the United States. There has been substantial evidence that environmental factors affect the risk of developing colorectal adenoma, precursors of colorectal cancer.

Objective: This study was conducted to investigate whether serum lipids are associated with risk of incident, sporadic colorectal adenomatous polyps.

Methods: Data were analyzed from a case-control study of incident, sporadic colorectal adenoma (n = 534) and colonoscopy negative controls (n = 644) conducted in Minnesota between 1990 and 1994. Self-administered questionnaires were used to collect demographic, dietary, and lifestyle information from all participants. Blood samples were drawn from participants to measure information on serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), and triglycerides. Multivariate logistic regression analyses were conducted to investigate the associations between serum lipid levels and risk of incident, sporadic colorectal adenoma.

Results: In the crude analyses, higher levels of HDL-C were associated with lower risk of colorectal adenoma (odds ratio (OR) = 0.57; 95% confidence interval (CI): 0.41, 0.80, highest quartile vs. lowest quartile) and higher levels of LDL-C were associated with increased risk of colorectal adenoma (OR = 1.46; CI: 1.04-2.04, highest quartile vs. lowest quartile). Total cholesterol, VLDL-C, and triglycerides were not associated with risk of colorectal adenoma. In the multivariable analysis, higher levels of HDL-C were not associated with risk of colorectal adenoma (OR = 0.77; CI: 0.47-1.27, highest quartile vs. lowest quartile) and higher levels of LDL-C were not associated with risk of colorectal adenoma (OR = 1.05; CI: 0.68-1.61).

Discussions: Overall, serum lipid levels were not associated with risk for incident, sporadic colorectal adenoma. After adjustment for risk factors that tend to play a role in determining blood lipid levels, the associations of HDL-C and LDL-C were attenuated to close to the null value. These findings suggest that blood lipid levels may not affect risk for colorectal neoplasms; however, it is possible that exposures that influence HDL and LDL cholesterol levels may be more relevant to risk for the disease.

Introduction

Colorectal cancer is a significant public health issue and is the third most common cancer in the United States [15, 31]. Because of limited treatment at advanced stage of colorectal cancer, prospects of colorectal cancer must focus on prevention and early detection [15]. Despite abundant knowledge on genetic pathways of progression from colorectal adenoma to cancer, findings from migration studies suggest the dominant role of environmental factors in colorectal pathogenicity [1, 2, 15, 52, 53, 60, 62, 66, 68, 72, 75]. Environmental factors such as western dietary patterns, obesity, physical inactivity, high alcohol consumption, and smoking are positively associated with colorectal cancer [159-162].

The dietary factors and unhealthy lifestyle factors associated with colorectal cancer are also found to influence serum lipid levels unfavorably [5-9]. Thus, dyslipidemia, abnormal levels of serum lipid levels, could be consequences of these risk factors of colorectal cancer, rather than direct risk factors for colorectal carcinogenesis [10]. Serum lipid levels have been associated with neoplastic processes such as inflammation, oxidative stress, and insulin resistance [11-14].

Although several epidemiological studies have investigated associations of lipid serums and colorectal adenoma, findings from them have been inconclusive. Most previous studies were small and have only investigated levels of total cholesterol. In addition, most of the previous studies did not control for important factors. Few studies investigated associations according to adenoma characteristics.

Because of inconsistency of results on associations between serum lipids and colorectal adenoma, the extent of the roles of dyslipidemia in colorectal neoplasia can not

be determined. In this study, we examine the associations with adequate adjustment for risk factors that are important in the etiology of colorectal cancer. In addition, we also assess the associations according to adenoma characteristics. To address this literature gap, herein we report the results of a colonoscopy-based case-control study of serum lipids and incident, sporadic colorectal adenomas.

Materials and Methods

Case-control study

This was a colonoscopy-based case-control study of incident, sporadic colorectal adenoma conducted by the Cancer Prevention Research Unit (CPRU) as collaboration of the University of Minnesota and Digestive Healthcare (DH), a multisite private gastroenterology clinic located in the Minneapolis metropolitan areas. Participants in the study were recruited from among patients with no prior history of colorectal neoplasms who were scheduled to undergo outpatient, elective colonoscopy in DH clinics. The eligibility criteria for the study included: between 30-74 years of age, English-proficient, and willing to participate. Participants with previous colorectal adenomas, ulcerative colitis, familial polyposis, Crohn's Disease, Gardner's Disease, bowel re-section, and cancer other than non-melanoma skin cancer were excluded. The detailed protocol of the CPRU study was published previously [163].

Data Collection

Before undergoing colonoscopy, all patients filled out mailed questionnaires on demographics, family history of colorectal adenoma, reproductive history (women), self-measured anthropometrics, physical activity, alcohol consumption, tobacco use, and reason for colonoscopy. Dietary information was collected via a Willett 153-item food

semi-quantitative frequency questionnaire.

Prior to undergoing colonoscopy, all participants were asked to fast for 12 hours and polyethylene glycol was used to clean the bowel of the participants. Blood samples were drawn from each participant. Serum and plasma were separated based on standard protocol and plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), triglycerides, and 25-hydroxy-vitamin D_3 were measured. For quality control, blinded duplicate blood specimens were drawn and analyzed on every 20^{th} subject.

For colorectal polyps found on colonoscopy, their colon site and *in vivo* size and shape were recorded. Polyp histologic characteristics (adenoma, hyperplastic or other) were recorded. If an adenoma, the histologic type, and degree of dysplasia were recorded by one study pathologist using the diagnostic criteria used in the National Polyp Study [164]. Depending upon the colonoscopy/pathology findings, each participant was classified into a colorectal adenoma group (designated as cases), a hyperplastic polyp only group, or a colonoscopy-negative group (designated as controls). Subjects with missing total cholesterol levels (33 colorectal adenoma cases and 44 colonoscopy-negative controls) or who did not complete their food frequency questionnaire (7 colorectal adenoma cases and 19 colonoscopy-negative controls) were also excluded from the study. After exclusions, the final study sample size for the analysis reported herein was 534 colorectal adenoma cases and 644 colonoscopy-negative controls.

Statistical Analysis

The baseline characteristics of cases and controls were compared using the chi-square test for categorical variables and the *t* test for continuous variables. Continuous

variables that were not normally distributed were normalized by transforming them by the natural logarithm prior to inference testing.

Among cases and controls, the lipids were categorized into quartiles based on the distributions in the controls. The first, or lowest, quartiles of the lipids served as the respective reference categories. Unconditional logistic regression was conducted to analyze the associations between quartiles of lipids and risk of colorectal adenoma, with appropriate covariates, as described below. Trend tests were also calculated based on the median of each lipid quartile. In addition, unconditional logistic regression was conducted to analyze the associations between quartiles of lipids and risk for colorectal adenomas according to adenoma characteristics such as colon site, multiplicity, size, shape, histologic type, and degree of dysplasia. We also examined multivariable-adjusted associations stratified by sex, age, family history of colorectal cancer in a first-degree family relative, and regular use of non-steroidal anti-inflammatory drugs. Possible interactions were assessed by comparing stratum-specific odds ratios and conducting Wald's Test.

Multivariable-adjusted models were built as follows: Based on biological plausibility and previous literature, the following variables were considered as potential confounders: age, sex, body mass index, waist-to-hip ratio, family history of colorectal cancer in a first-degree relative, use of hormone replacement therapy (for women), regular use of non-steroidal anti-inflammatory drugs, pack-years of smoking, alcohol consumption, metabolic equivalent task hours of physical activity, total energy intake (kcal), intake of saturated fat, intake of monounsaturated fat, intake of polyunsaturated fat, intake of total red and processed meats, intake of fiber, intake of calcium, and intake

of 25-hydroxyvitamin D_3. The criteria for inclusion in the final models were: 1) biological plausibility, 2) whether it fit in the model at a significance level of $p \leq 0.10$, and 3) whether its inclusion in the model changed the OR for the primary exposure variable by $\geq 10\%$. Macronutrient variables were energy-adjusted using the residual method. Total energy-adjusted residuals of saturated fat and polyunsaturated fat were forced into the model. Multicollinearity was assessed with Pearson correlation coefficients, conditional index, and variation inflation factors among the covariates. Covariates included in the final model were: age, sex, body mass index, family history of colorectal cancer in a first-degree family relative, use of hormone replacement therapy, regular use of non-steroidal anti-inflammatory drugs, pack-years of smoking, alcohol consumption, metabolic equivalent task hours of physical activity, total energy intake (kcal), intake of saturated fat, intake of polyunsaturated fat, and intake of total red and processed meats.

All statistical analyses were two-sided, with a cut-off level of p-value <0.05 used to assess statistical significance. The statistical analyses were conducted using SAS Software Version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Selected baseline characteristics of the cases and controls are presented in Table 1. Compared to controls, cases tended to be older, more likely to be male, have a higher waist-to- hip ratio, consume more alcohol, to have smoked more, and to have consumed more total fat, saturated fat, monounsaturated fat, and polyunsaturated fats. Controls were more likely to have family history of colorectal cancer in a first-degree family relative, and, if a woman, more likely to take hormone replacement therapy. Mean serum

total cholesterol level, very-low-density lipoprotein cholesterol level, and triglycerides level did not differ between cases and controls. Compared to controls, on average, cases had lower high-density lipoprotein and higher low-density lipoprotein cholesterol levels.

Thirty-one percent of cases had multiple colorectal adenomas, 30% had at least one colorectal adenoma in the right colon, and 34% had a large (≥1.0 cm) colorectal adenoma. In addition, in 51% of cases, the largest adenoma was of sessile shape, in 33% the largest adenoma was of villous or tubulovillous histologic type, and in 49% the largest adenoma had moderate or severe dysplasia (Data not shown).

As seen in Table 2, the univariate odds ratio comparing subjects in the highest to those in the lowest quartile of total cholesterol levels was 1.15 (95% CI = 0.83-1.60; P_{trend} = 0.0002). Higher HDL and LDL cholesterol levels were statistically significantly associated with approximate 40 percent lower and 50 percent higher in risk of colorectal adenoma, respectively. VLDL cholesterol and triglycerides were not associated with risk for colorectal adenoma. The associations of HDL and LDL cholesterol levels with adenomas did not differ substantially according to adenoma characteristics; however, the sample size was relatively small for these analyses.

In the multivariable analyses (Table 3), higher HDL and LDL cholesterol levels were not substantially or statistically significantly associated with risk of colorectal adenoma (highest vs. lowest quartile of HDL cholesterol levels: OR = 0.77; 95% CI: 0.47, 1.27, P_{trend} = 0.30; highest vs. lowest quartile of LDL cholesterol levels: OR = 1.05; 95% CI: 0.68, 1.61, P_{trend} = 0.95). In addition, higher levels of total cholesterol, VLDL cholesterol, and triglycerides were not associated with risk of colorectal adenoma after multivariable adjustment (highest vs. lowest quartile of total cholesterol levels:

OR = 0.84, 95% CI: 0.55, 1.29, P_{trend} = 0.38; highest vs. lowest quartile of VLDL cholesterol levels: OR = 0.83, 95% CI: 0.54, 1.29, P_{trend} = 0.72; highest vs. lowest quartile of triglycerides levels: OR = 0.95, 95% CI: 0.61, 1.47).

We also examined whether associations of lipid levels with colorectal adenoma were modified by selected risk factors for colorectal neoplasms (Table 4). The second quartile of VLDL cholesterol levels (12-18 mg/dl) were associated with statistically significant lower in adenoma risk among women and those who did not regularly take an NSAID; however, the tests for trend and interactions were not statistically significant (women: OR = 0.47, 95% CI: 0.26,0.85; non-NSAID users: OR= 0.57, 95% CI: 0.36, 0.91). There were no substantial differences in the associations of VLDL cholesterol-adenoma association according age or family history of colorectal cancer in a first-degree family relative. Also, the associations of higher total-, HDL-, LDL-cholesterol, and triglycerides levels with adenoma did not differ substantially by sex, age, family history of colorectal cancer in a first-degree family relative, and regular use of NSAID.

Discussion

The primary conclusion is that, overall, we did not find blood lipid levels to be associated with risk for incident, sporadic colorectal adenoma. In our crude analyses, higher levels of HDL and LDL cholesterol were associated with lower and higher risk for adenoma, respectively. However, after adjustment for risk factors that tend to play a role in determining blood lipid levels, the associations were attenuated to close to the null value. These findings suggest that blood lipid levels may not affect risk for colorectal neoplasms; however, it is possible that exposures that influence HDL and LDL cholesterol levels may be more relevant to the risk for the disease. Our findings also

suggest that for women and non-NSAID users above the first quartile of VLDL cholesterol levels, there was a suggestion for lower risk of adenoma. However, there is no known biological plausibility for the inverse associations. There was no definable pattern of any association across the quartiles, and the tests for trend and interaction were not statistically significant, suggesting that this may have been a chance finding.

In previously published epidemiologic studies, the associations of higher total cholesterol levels with colorectal adenoma were inconsistent, showing either statistically significant positive associations [17, 18], or no associations at all [15, 16, 23, 28]. Findings from previous studies on higher levels of HDL cholesterol and colorectal adenoma found either an inverse association [18], or no association [20, 23]. Of nine studies that investigated associations of high triglycerides levels with colorectal adenoma, six found statistically significant positive associations [15, 19, 20, 22, 23, 27] and three found no associations [15, 16, 27]. Findings on associations of LDL cholesterol levels with colorectal adenoma have also been inconsistent, with one study finding a statistically significant positive association [107] and two findings showing no associations [18, 19, 165]. Data on VLDL cholesterol levels are scarce. The inconsistent results of the associations between cholesterol levels and colorectal adenoma may have been due to omitted variable bias from studies that did not adjust for important macronutrients that play a role in determining blood lipid levels. Dietary saturated fat, a macronutrient, increases total cholesterol levels by raising both HDL cholesterol levels and LDL cholesterol levels [166, 167]. In trials in which monounsaturated fat and polyunsaturated fat were eaten in place of carbohydrates, LDL cholesterol levels decreased and HDL cholesterol levels increased [168]. Several studies of triglycerides

and colorectal adenoma did not adjust for family history of colorectal cancer. In our study, we examined the associations of lipids and risk of colorectal adenoma adjusted for saturated fat, polyunsaturated fat, family history of colorectal cancer and other demographic, medication, lifestyle, and dietary factors. Adequate adjustment for confounding factors may explain our null findings.

Our study had several limitations. We had limited sample size for statistical analyses; however, our study is the largest to date to investigate associations according to multiple adenoma characteristics and biological plausible potential effect modifiers. Our study population may not be representative of the general population as they all were receiving colonoscopies and most were older whites in the state of Minnesota. Colonoscopy controls in the study (which was conducted between 1991 and 1994, before the use of colonoscopies for routine screening purposes) represent a highly selected group of participants, a substantial proportion of whom were either symptomatic or had known risk factors such as positive family history of colorectal cancer. Because most participants in our study had an indication for undergoing a colonoscopy, serum lipids and exposure to other risk factors may have been similar between cases and controls, resulting in attenuation of the results toward the null. One of the strengths of this study was the verification of adenoma- and hyperplastic polyp-free status of controls by colonoscopy, thereby minimizing outcome misclassification. Another strength was collecting detailed information on multiple covariates before case-control status was ascertained, which helped reduce both recall bias and unmeasured confounding.

In conclusion, our findings do not support the hypothesis that higher levels of serum lipids are associated with risk of incident, sporadic colorectal adenoma. However,

it is possible that higher levels of HDL and LDL cholesterol levels are consequences of the risk factors that are associated with colorectal adenoma, suggesting that exposures that influence HDL and LDL cholesterol levels may be more relevant to risk for the disease.

CHAPTER 3: CONCLUSIONS

Summary

We did not find higher levels of serum lipids to be associated with risk of incident, sporadic colorectal adenoma. In crude analyses, higher HDL and LDL cholesterol levels were statistically significantly associated with lower and higher risk, respectively, with incident, sporadic colorectal adenoma. After multivariable adjustment, the associations become attenuated to close to the null value and were no longer statistically significant. These findings suggest that higher levels of HDL and LDL cholesterol are not risk factors for colorectal adenoma, but are rather consequences of the covariates we adjusted for in the final model.

Our findings also suggest that for women and non-NSAID users above the first quartile of VLDL cholesterol levels, there was a suggestion for lower risk of adenoma. However, there is no known biological plausibility for the inverse associations. There was no definable pattern of any association across the quartiles, and the tests for trend and interaction were not statistically significant, suggesting that this may have been a chance finding.

Public Health Implications

Our findings have several public health implications. As more countries are adopting western diets, hyperlipidemia and dyslipidemia are increasingly common globally, and are becoming increasingly important public health issues for chronic diseases [53]. In 2008, colorectal cancer was the third most common cancer among men and second most common cancer among women worldwide [169]. In 2010, colorectal cancer was the third most common cancer in the United States [31]. Due to limited

treatment at advanced stage of colorectal cancer, the prospects of the cancer should focus on prevention and early detection [15]. A few previous studies suggested that higher levels of serum lipids increase risk of colorectal adenoma, known precursors to colorectal cancer [148, 155]. However, overall, total-, HDL-, LDL-cholesterol, and triglycerides have yielded inconsistent findings [15-22, 159]. To our knowledge, no previous studies have investigated an association of higher VLDL cholesterol level with colorectal adenoma.

Overall, we did not find blood lipid levels to be associated with risk for incident, sporadic colorectal adenoma. In our crude analyses, higher levels of HDL and LDL cholesterol were associated with lower and higher risk for adenoma, respectively. However, after adjustment for risk factors that tend to play a role in determining blood lipid levels, the associations were attenuated to close to the null value. These findings suggest that blood lipid levels may not affect risk for colorectal neoplasms; however, it is possible that exposures that influence HDL and LDL cholesterol levels may be more relevant to the risk for the disease.

Possible Future Directions

The findings of this study suggest several possible future research directions. Because our study sample focused primarily on participants of white race, studies are needed to investigate associations of higher serum lipids and colorectal adenoma among individuals of difference races. Because few studies investigated the association of higher VLDL cholesterol levels with risk of colorectal adenoma, more data on potential associations and mechanisms are needed. Our findings of an inverse association of VLDL

with colorectal adenoma among women and non-NSAID users also require replication and explanation if it can be considered plausible.

REFERENCES

1. Arnold, M., O. Razum, and J.W. Coebergh, *Cancer risk diversity in non-western migrants to Europe: An overview of the literature.* Eur J Cancer, 2010. **46**(14): p. 2647-59.
2. Singh, G.K. and B.A. Miller, *Health, life expectancy, and mortality patterns among immigrant populations in the United States.* Can J Public Health, 2004. **95**(3): p. I14-21.
3. Kim, D.H. and Y.O. Ahn, *Molecular epidemiology of colon cancer.* Cancer Res Treat, 2004. **36**(2): p. 93-9.
4. McMichael, A.J. and G.G. Giles, *Colorectal cancer.* Cancer Surv, 1994. **19-20**: p. 77-98.
5. Craig, W.Y., G.E. Palomaki, and J.E. Haddow, *Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data.* BMJ, 1989. **298**(6676): p. 784-8.
6. Lee, S.A., et al., *Stability and reliability of plasma level of lipid biomarkers and their correlation with dietary fat intake.* Dis Markers, 2008. **24**(2): p. 73-9.
7. Hardman, A.E., *Interaction of physical activity and diet: implications for lipoprotein metabolism.* Public Health Nutr, 1999. **2**(3A): p. 369-76.
8. Kasim-Karakas, S.E., et al., *Changes in plasma lipoproteins during low-fat, high-carbohydrate diets: effects of energy intake.* Am J Clin Nutr, 2000. **71**(6): p. 1439-47.
9. Frohlich, J.J., *Effects of alcohol on plasma lipoprotein metabolism.* Clin Chim Acta, 1996. **246**(1-2): p. 39-49.
10. van Duijnhoven, F.J., et al., *Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition.* Gut, 2011.
11. Esteve, E., W. Ricart, and J.M. Fernandez-Real, *Dyslipidemia and inflammation: an evolutionary conserved mechanism.* Clin Nutr, 2005. **24**(1): p. 16-31.
12. Avramoglu, R.K., H. Basciano, and K. Adeli, *Lipid and lipoprotein dysregulation in insulin resistant states.* Clin Chim Acta, 2006. **368**(1-2): p. 1-19.
13. Kontush, A., et al., *A normotriglyceridemic, low HDL-cholesterol phenotype is characterised by elevated oxidative stress and HDL particles with attenuated antioxidative activity.* Atherosclerosis, 2005. **182**(2): p. 277-85.
14. Vekic, J., et al., *Association of oxidative stress and PON1 with LDL and HDL particle size in middle-aged subjects.* Eur J Clin Invest, 2007. **37**(9): p. 715-23.
15. Chung, Y.W., et al., *Association of obesity, serum glucose and lipids with the risk of advanced colorectal adenoma and cancer: a case-control study in Korea.* Dig Liver Dis, 2006. **38**(9): p. 668-72.
16. Kono, S., et al., *Serum lipids and colorectal adenoma among male self-defence officials in northern Kyushu, Japan.* Int J Epidemiol, 1990. **19**(2): p. 274-8.
17. Kamiya, N., T. Sakata, and N. Takenaga, *[The risk of colorectal adenomatous polyp in relation to serum total cholesterol levels in Japanese men classified by age group]*. Sangyo Eiseigaku Zasshi, 2000. **42**(3): p. 97-101.

18. Bayerdorffer, E., et al., *Decreased high-density lipoprotein cholesterol and increased low-density cholesterol levels in patients with colorectal adenomas.* Ann Intern Med, 1993. **118**(7): p. 481-7.
19. Kono, S., et al., *Serum lipids and left-sided adenomas of the large bowel: an extended study of self-defense officials in Japan.* Cancer Causes Control, 1993. **4**(2): p. 117-21.
20. Liu, C.S., et al., *Central obesity and atherogenic dyslipidemia in metabolic syndrome are associated with increased risk for colorectal adenoma in a Chinese population.* BMC Gastroenterol, 2010. **10**: p. 51.
21. Park, S.K., et al., *Association of serum lipids and glucose with the risk of colorectal adenomatous polyp in men: a case-control study in Korea.* J Korean Med Sci, 2000. **15**(6): p. 690-5.
22. Otani, T., et al., *Serum triglycerides and colorectal adenoma in a case-control study among cancer screening examinees (Japan).* Cancer Causes Control, 2006. **17**(10): p. 1245-52.
23. Bird, C.L., et al., *Serum lipids and adenomas of the left colon and rectum.* Cancer Epidemiol Biomarkers Prev, 1996. **5**(8): p. 607-12.
24. Mannes, G.A., et al., *Relation between the frequency of colorectal adenoma and the serum cholesterol level.* N Engl J Med, 1986. **315**(26): p. 1634-8.
25. Ashbeck, E.L., et al., *Components of metabolic syndrome and metachronous colorectal neoplasia.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(4): p. 1134-43.
26. Kim, J.H., et al., *Is metabolic syndrome a risk factor for colorectal adenoma?* Cancer Epidemiol Biomarkers Prev, 2007. **16**(8): p. 1543-6.
27. Otake, S., et al., *Decreased levels of plasma adiponectin associated with increased risk of colorectal cancer.* World J Gastroenterol, 2010. **16**(10): p. 1252-7.
28. Tsilidis, K.K., et al., *Metabolic syndrome components and colorectal adenoma in the CLUE II cohort.* Cancer Causes Control, 2010. **21**(1): p. 1-10.
29. Society, A.C. *What is colorectal cancer?* 2010 [cited 2010 August 1]; Available from: http://www.cancer.org/Cancer/ColonandRectumCancer/DetailedGuide/colorectal-cancer-what-is-colorectal-cancer.
30. Society, A.C. *What is colorectal cancer?* . 2010; Available from: http://www.cancer.org/Cancer/ColonandRectumCancer/DetailedGuide/colorectal-cancer-what-is-colorectal-cancer.
31. Society, A.C., *Cancer Facts & Figures 2010.* 2010.
32. Jemal, A., et al., *Cancer statistics, 2010.* CA Cancer J Clin, 2010. **60**(5): p. 277-300.
33. Altekruse SF, K.C., Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2007.* Available from: http://seer.cancer.gov/csr/1975_2007/.
34. Theuer, C.P., et al., *Racial and ethnic colorectal cancer patterns affect the cost-effectiveness of colorectal cancer screening in the United States.* Gastroenterology, 2001. **120**(4): p. 848-56.

35. Rise LAG, E.M., Kosary CL, et al. eds. *SEER Cancer Statistics Review, 1975-2000*. 2003 [cited 2010 9/1/2010]; Available from: http://seer.cancer.gov/csr/1975-2000.
36. Ghafoor, A., et al., *Cancer statistics for African Americans.* CA Cancer J Clin, 2002. **52**(6): p. 326-41.
37. Troisi, R.J., A.N. Freedman, and S.S. Devesa, *Incidence of colorectal carcinoma in the U.S.: an update of trends by gender, race, age, subsite, and stage, 1975-1994.* Cancer, 1999. **85**(8): p. 1670-6.
38. Parker, S.L., et al., *Cancer statistics by race and ethnicity.* CA Cancer J Clin, 1998. **48**(1): p. 31-48.
39. Marcella, S. and J.E. Miller, *Racial differences in colorectal cancer mortality. The importance of stage and socioeconomic status.* J Clin Epidemiol, 2001. **54**(4): p. 359-66.
40. Merrill, R.M., D.E. Henson, and L.A. Ries, *Conditional survival estimates in 34,963 patients with invasive carcinoma of the colon.* Dis Colon Rectum, 1998. **41**(9): p. 1097-106.
41. Clegg, L.X., et al., *Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology, and End Results) Program population-based study.* Arch Intern Med, 2002. **162**(17): p. 1985-93.
42. Wingo, P.A., et al., *Long-term cancer patient survival in the United States.* Cancer Epidemiol Biomarkers Prev, 1998. **7**(4): p. 271-82.
43. Mayberry, R.M., et al., *Determinants of black/white differences in colon cancer survival.* J Natl Cancer Inst, 1995. **87**(22): p. 1686-93.
44. Mandelblatt, J., et al., *The late-stage diagnosis of colorectal cancer: demographic and socioeconomic factors.* Am J Public Health, 1996. **86**(12): p. 1794-7.
45. Wudel, L.J., Jr., et al., *Disparate outcomes in patients with colorectal cancer: effect of race on long-term survival.* Arch Surg, 2002. **137**(5): p. 550-4; discussion 554-6.
46. Freeman, H.P. and T.A. Alshafie, *Colorectal carcinoma in poor blacks.* Cancer, 2002. **94**(9): p. 2327-32.
47. Gellad, Z.F. and D. Provenzale, *Colorectal cancer: national and international perspective on the burden of disease and public health impact.* Gastroenterology, 2010. **138**(6): p. 2177-90.
48. Parkin, D.M., et al., *Global cancer statistics, 2002.* CA Cancer J Clin, 2005. **55**(2): p. 74-108.
49. Vainio, H. and A.B. Miller, *Primary and secondary prevention in colorectal cancer.* Acta Oncol, 2003. **42**(8): p. 809-15.
50. Center, M.M., et al., *Worldwide variations in colorectal cancer.* CA Cancer J Clin, 2009. **59**(6): p. 366-78.
51. Wolpin, B.M., et al., *Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer.* J Clin Oncol, 2009. **27**(2): p. 176-85.
52. Moradi, T., et al., *Cancer risk among Scandinavian immigrants in the US and Scandinavian residents compared with US whites, 1973-89.* Eur J Cancer Prev, 1998. **7**(2): p. 117-25.

53. Stirbu, I., et al., *Cancer mortality rates among first and second generation migrants in the Netherlands: Convergence toward the rates of the native Dutch population.* Int J Cancer, 2006. **119**(11): p. 2665-72.
54. Brussaard, J.H., et al., *Nutrition and health among migrants in The Netherlands.* Public Health Nutr, 2001. **4**(2B): p. 659-64.
55. Reijneveld, S.A., *Reported health, lifestyles, and use of health care of first generation immigrants in The Netherlands: do socioeconomic factors explain their adverse position?* J Epidemiol Community Health, 1998. **52**(5): p. 298-304.
56. Ziegler, R.G., S.S. Devesa, and J.F. Fraumeni, Jr., *Epidemiologic patterns of colorectal cancer.* Important Adv Oncol, 1986: p. 209-32.
57. Ponz de Leon, M. and C. Di Gregorio, *Pathology of colorectal cancer.* Dig Liver Dis, 2001. **33**(4): p. 372-88.
58. Kim, E.C. and P. Lance, *Colorectal polyps and their relationship to cancer.* Gastroenterol Clin North Am, 1997. **26**(1): p. 1-17.
59. Yang, S.Y., et al., *Association between colorectal adenoma and coronary atherosclerosis detected by CT coronary angiography in Korean men; a cross-sectional study.* J Gastroenterol Hepatol, 2010. **25**(11): p. 1795-9.
60. Fearon, E.R., *Molecular genetic studies of the adenoma-carcinoma sequence.* Adv Intern Med, 1994. **39**: p. 123-47.
61. Alberici, P. and R. Fodde, *The role of the APC tumor suppressor in chromosomal instability.* Genome Dyn, 2006. **1**: p. 149-70.
62. Goss, K.H. and J. Groden, *Biology of the adenomatous polyposis coli tumor suppressor.* J Clin Oncol, 2000. **18**(9): p. 1967-79.
63. Hamilton, S.R., *The adenoma-adenocarcinoma sequence in the large bowel: variations on a theme.* J Cell Biochem Suppl, 1992. **16G**: p. 41-6.
64. Luo, F., et al., *Mutant K-ras promotes carcinogen-induced murine colorectal tumourigenesis, but does not alter tumour chromosome stability.* J Pathol, 2010.
65. Luo, F., et al., *K-ras exon 4A has a tumour suppressor effect on carcinogen-induced murine colonic adenoma formation.* J Pathol, 2010. **220**(5): p. 542-50.
66. Boughdady, I.S., et al., *K-ras gene mutations in adenomas and carcinomas of the colon.* Surg Oncol, 1992. **1**(4): p. 275-82.
67. Barry, E.L., et al., *K-ras mutations in incident sporadic colorectal adenomas.* Cancer, 2006. **106**(5): p. 1036-40.
68. Cho, K.R. and B. Vogelstein, *Genetic alterations in the adenoma--carcinoma sequence.* Cancer, 1992. **70**(6 Suppl): p. 1727-31.
69. Froggatt, N.J., S.H. Leveson, and R.C. Garner, *Low frequency and late occurrence of p53 and dcc aberrations in colorectal tumours.* J Cancer Res Clin Oncol, 1995. **121**(1): p. 7-15.
70. Bernet, A. and P. Mehlen, *Dependence receptors: when apoptosis controls tumor progression.* Bull Cancer, 2007. **94**(4): p. E12-7.
71. Bamias, A.T., et al., *Prognostic significance of the deleted in colorectal cancer gene protein expression in high-risk resected gastric carcinoma.* Cancer Invest, 2003. **21**(3): p. 333-40.
72. Vidaurreta, M., et al., *Colorectal carcinoma prognosis can be predicted by alterations in gene p53 exons 5 and 8.* Int J Colorectal Dis, 2008. **23**(6): p. 581-6.

73. Ronchetto, F., *[Genetic alterations and molecular mechanisms underlying colorectal tumorigenesis]*. Minerva Med, 1998. **89**(5): p. 163-8.
74. Giaretti, W., et al., *Intratumor heterogeneity of k-ras and p53 mutations among human colorectal adenomas containing early cancer.* Anal Cell Pathol, 2000. **21**(2): p. 49-57.
75. Abdel-Rahman, W.M., J.P. Mecklin, and P. Peltomaki, *The genetics of HNPCC: application to diagnosis and screening.* Crit Rev Oncol Hematol, 2006. **58**(3): p. 208-20.
76. Wernli, K.J., et al., *Body size, IGF and growth hormone polymorphisms, and colorectal adenomas and hyperplastic polyps.* Growth Horm IGF Res, 2010. **20**(4): p. 305-9.
77. Sandhu, M.S., D.B. Dunger, and E.L. Giovannucci, *Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer.* J Natl Cancer Inst, 2002. **94**(13): p. 972-80.
78. Jones, J.I. and D.R. Clemmons, *Insulin-like growth factors and their binding proteins: biological actions.* Endocr Rev, 1995. **16**(1): p. 3-34.
79. Giovannucci, E., *Insulin, insulin-like growth factors and colon cancer: a review of the evidence.* J Nutr, 2001. **131**(11 Suppl): p. 3109S-20S.
80. Stein, B., et al., *Body mass index as a predictor of colorectal neoplasia in ethnically diverse screening population.* Dig Dis Sci, 2010. **55**(10): p. 2945-52.
81. Jacobs, E.T., et al., *Association between body size and colorectal adenoma recurrence.* Clin Gastroenterol Hepatol, 2007. **5**(8): p. 982-90.
82. MacInnis, R.J., et al., *Body size and composition and colon cancer risk in women.* Int J Cancer, 2006. **118**(6): p. 1496-500.
83. Wolf, L.A., et al., *Do factors related to endogenous and exogenous estrogens modify the relationship between obesity and risk of colorectal adenomas in women?* Cancer Epidemiol Biomarkers Prev, 2007. **16**(4): p. 676-83.
84. Giovannucci, E., et al., *Physical activity, obesity, and risk for colon cancer and adenoma in men.* Ann Intern Med, 1995. **122**(5): p. 327-34.
85. Lee, H.L., et al., *[Abdominal obesity, insulin resistance, and the risk of colonic adenoma]*. Korean J Gastroenterol, 2007. **49**(3): p. 147-51.
86. Morois, S., et al., *Anthropometric factors in adulthood and risk of colorectal adenomas: The French E3N-EPIC prospective cohort.* Am J Epidemiol, 2010. **172**(10): p. 1166-80.
87. Kune, G.A., S. Bannerman, and L.F. Watson, *Attributable risk for diet, alcohol, and family history in the Melbourne Colorectal Cancer Study.* Nutr Cancer, 1992. **18**(3): p. 231-5.
88. Randi, G., et al., *Dietary patterns and the risk of colorectal cancer and adenomas.* Nutr Rev, 2010. **68**(7): p. 389-408.
89. Breuer-Katschinski, B., et al., *Colorectal adenomas and diet: a case-control study. Colorectal Adenoma Study Group.* Dig Dis Sci, 2001. **46**(1): p. 86-95.
90. Bernstein, C.N. *DNA Damage and Cancer*. 2009; Available from: http://webcache.googleusercontent.com/search?q=cache:onZBMQYce_4J:www.scitopics.com/DNA_Damage_and_Cancer.html+does+high+fat+diet+lead+to+increased+bile+acid%3F&cd=2&hl=en&ct=clnk&gl=us.

91. Bernstein, H., et al., *Bile acids as endogenous etiologic agents in gastrointestinal cancer.* World J Gastroenterol, 2009. **15**(27): p. 3329-40.
92. Lee, D.H., et al., *Heme iron, zinc, alcohol consumption, and colon cancer: Iowa Women's Health Study.* J Natl Cancer Inst, 2004. **96**(5): p. 403-7.
93. Reddy, B.S., et al., *Effect of high-fat, high-beef diet and of mode of cooking of beef in the diet on fecal bacterial enzymes and fecal bile acids and neutral sterols.* J Nutr, 1980. **110**(9): p. 1880-7.
94. Hill, M.J., *Bile flow and colon cancer.* Mutat Res, 1990. **238**(3): p. 313-20.
95. Bernstein, C., et al., *DNA repair/pro-apoptotic dual-role proteins in five major DNA repair pathways: fail-safe protection against carcinogenesis.* Mutat Res, 2002. **511**(2): p. 145-78.
96. Crowley-Weber, C.L., et al., *Nicotine increases oxidative stress, activates NF-kappaB and GRP78, induces apoptosis and sensitizes cells to genotoxic/xenobiotic stresses by a multiple stress inducer, deoxycholate: relevance to colon carcinogenesis.* Chem Biol Interact, 2003. **145**(1): p. 53-66.
97. Ferrucci, L.M., et al., *Dietary meat intake in relation to colorectal adenoma in asymptomatic women.* Am J Gastroenterol, 2009. **104**(5): p. 1231-40.
98. Voskuil, D.W., et al., *Meat consumption and meat preparation in relation to colorectal adenomas among sporadic and HNPCC family patients in The Netherlands.* Eur J Cancer, 2002. **38**(17): p. 2300-8.
99. Sinha, R., et al., *High concentrations of the carcinogen 2-amino-1-methyl-6-phenylimidazo- [4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method.* Cancer Res, 1995. **55**(20): p. 4516-9.
100. Sinha, R., et al., *Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness.* Food Chem Toxicol, 1998. **36**(4): p. 289-97.
101. Sinha, R., et al., *Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings.* Food Chem Toxicol, 1998. **36**(4): p. 279-87.
102. Rohrmann, S., S. Hermann, and J. Linseisen, *Heterocyclic aromatic amine intake increases colorectal adenoma risk: findings from a prospective European cohort study.* Am J Clin Nutr, 2009. **89**(5): p. 1418-24.
103. Asano, T. and R.S. McLeod, *Dietary fibre for the prevention of colorectal adenomas and carcinomas.* Cochrane Database Syst Rev, 2002(2): p. CD003430.
104. Martinez, M.E., *Primary prevention of colorectal cancer: lifestyle, nutrition, exercise.* Recent Results Cancer Res, 2005. **166**: p. 177-211.
105. Millen, A.E., et al., *Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial.* Am J Clin Nutr, 2007. **86**(6): p. 1754-64.
106. Carroll, C., et al., *Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis.* Clin Ther, 2010. **32**(5): p. 789-803.
107. Ahearn, T.U., et al., *A randomized clinical trial of the effects of supplemental calcium and vitamin D3 on markers of their metabolism in normal mucosa of colorectal adenoma patients.* Cancer Res, 2011. **71**(2): p. 413-23.
108. Peterlik, M., W.B. Grant, and H.S. Cross, *Calcium, vitamin D and cancer.* Anticancer Res, 2009. **29**(9): p. 3687-98.

109. Kallay, E., et al., *Molecular and functional characterization of the extracellular calcium-sensing receptor in human colon cancer cells.* Oncol Res, 2003. **13**(12): p. 551-9.
110. McCullough, M.L. and E.L. Giovannucci, *Diet and cancer prevention.* Oncogene, 2004. **23**(38): p. 6349-64.
111. Baron, J.A., et al., *Calcium supplements and colorectal adenomas. Polyp Prevention Study Group.* Ann N Y Acad Sci, 1999. **889**: p. 138-45.
112. Dusso, A.S., A.J. Brown, and E. Slatopolsky, *Vitamin D.* Am J Physiol Renal Physiol, 2005. **289**(1): p. F8-28.
113. Gandini, S., et al., *Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma.* Int J Cancer, 2010.
114. Holt, P.R., et al., *Colonic epithelial cell proliferation decreases with increasing levels of serum 25-hydroxy vitamin D.* Cancer Epidemiol Biomarkers Prev, 2002. **11**(1): p. 113-9.
115. Cross, H.S., et al., *Vitamin D metabolism in human colon adenocarcinoma-derived Caco-2 cells: expression of 25-hydroxyvitamin D3-1alpha-hydroxylase activity and regulation of side-chain metabolism.* J Steroid Biochem Mol Biol, 1997. **62**(1): p. 21-8.
116. Wei, M.Y., et al., *Vitamin D and prevention of colorectal adenoma: a meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2008. **17**(11): p. 2958-69.
117. Halle, M. and M.H. Schoenberg, *Physical activity in the prevention and treatment of colorectal carcinoma.* Dtsch Arztebl Int, 2009. **106**(44): p. 722-7.
118. Slattery, M.L., *Physical activity and colorectal cancer.* Sports Med, 2004. **34**(4): p. 239-52.
119. Howard, R.A., et al., *Physical activity, sedentary behavior, and the risk of colon and rectal cancer in the NIH-AARP Diet and Health Study.* Cancer Causes Control, 2008. **19**(9): p. 939-53.
120. Hauret, K.G., et al., *Physical activity and reduced risk of incident sporadic colorectal adenomas: observational support for mechanisms involving energy balance and inflammation modulation.* Am J Epidemiol, 2004. **159**(10): p. 983-92.
121. Wolin, K.Y. and H. Tuchman, *Physical activity and gastrointestinal cancer prevention.* Recent Results Cancer Res, 2011. **186**: p. 73-100.
122. Huxley, R.R., et al., *The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence.* Int J Cancer, 2009. **125**(1): p. 171-80.
123. Hermann, S., S. Rohrmann, and J. Linseisen, *Lifestyle factors, obesity and the risk of colorectal adenomas in EPIC-Heidelberg.* Cancer Causes Control, 2009. **20**(8): p. 1397-408.
124. Liao, K.F., et al., *Association between rectosigmoid adenomas and cardiovascular risk factors: a hospital-based, cross-sectional study.* Ann Acad Med Singapore, 2009. **38**(7): p. 630-6.
125. Anderson, J.C., et al., *Smokers as a high-risk group: data from a screening population.* J Clin Gastroenterol, 2009. **43**(8): p. 747-52.

126. Giovannucci, E., *An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(7): p. 725-31.
127. Ji, B.T., et al., *Tobacco smoking and colorectal hyperplastic and adenomatous polyps.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(5): p. 897-901.
128. Woodson, K., et al., *Hormone replacement therapy and colorectal adenoma recurrence among women in the Polyp Prevention Trial.* J Natl Cancer Inst, 2001. **93**(23): p. 1799-805.
129. Hawk, E.T. and B. Levin, *Colorectal cancer prevention.* J Clin Oncol, 2005. **23**(2): p. 378-91.
130. Janne, P.A. and R.J. Mayer, *Chemoprevention of colorectal cancer.* N Engl J Med, 2000. **342**(26): p. 1960-8.
131. Giovannucci, E., *Modifiable risk factors for colon cancer.* Gastroenterol Clin North Am, 2002. **31**(4): p. 925-43.
132. Greenlee, R.T., et al., *Cancer statistics, 2000.* CA Cancer J Clin, 2000. **50**(1): p. 7-33.
133. Calle, E.E., et al., *Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women.* J Natl Cancer Inst, 1995. **87**(7): p. 517-23.
134. Grodstein, F., P.A. Newcomb, and M.J. Stampfer, *Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis.* Am J Med, 1999. **106**(5): p. 574-82.
135. Terry, M.B., et al., *Risk factors for advanced colorectal adenomas: a pooled analysis.* Cancer Epidemiol Biomarkers Prev, 2002. **11**(7): p. 622-9.
136. Murff, H.J., et al., *The interaction of age and hormone replacement therapy on colon adenoma risk.* Cancer Detect Prev, 2007. **31**(2): p. 161-5.
137. Ruder, E.H., et al., *Non-Steroidal Anti-Inflammatory Drugs and Colorectal Cancer Risk in a Large, Prospective Cohort.* Am J Gastroenterol, 2011.
138. Mantovani, A., et al., *Cancer-related inflammation.* Nature, 2008. **454**(7203): p. 436-44.
139. Danese, S. and A. Mantovani, *Inflammatory bowel disease and intestinal cancer: a paradigm of the Yin-Yang interplay between inflammation and cancer.* Oncogene, 2010. **29**(23): p. 3313-23.
140. Kasper, H.U., et al., *COX-2 expression and effects of COX-2 inhibition in colorectal carcinomas and their liver metastases.* Anticancer Res, 2010. **30**(6): p. 2017-23.
141. Eberhart, C.E., et al., *Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas.* Gastroenterology, 1994. **107**(4): p. 1183-8.
142. Cole, B.F., et al., *Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials.* J Natl Cancer Inst, 2009. **101**(4): p. 256-66.
143. Rostom, A., et al., *Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force.* Ann Intern Med, 2007. **146**(5): p. 376-89.

144. Potter, J.D., et al., *Colon cancer: a review of the epidemiology.* Epidemiol Rev, 1993. **15**(2): p. 499-545.
145. Willett, W.C., et al., *Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women.* N Engl J Med, 1990. **323**(24): p. 1664-72.
146. Bostick, R.M., et al., *Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States).* Cancer Causes Control, 1994. **5**(1): p. 38-52.
147. Leufkens, A.M., et al., *Cigarette smoking and colorectal cancer risk in the European prospective investigation into cancer and nutrition study.* Clin Gastroenterol Hepatol, 2011. **9**(2): p. 137-44.
148. Takahashi, H., et al., *Life style-related diseases of the digestive system: colorectal cancer as a life style-related disease: from carcinogenesis to medical treatment.* J Pharmacol Sci, 2007. **105**(2): p. 129-32.
149. Stemmermann, G.N., et al., *Adenomatous polyps and atherosclerosis: an autopsy study of Japanese men in Hawaii.* Int J Cancer, 1986. **38**(6): p. 789-94.
150. Paraf, F., J.C. Bouillot, and P. Bruneval, *[Cholesterol crystal embolisms in adenomatous polyposis coli].* Ann Pathol, 1999. **19**(2): p. 135-8.
151. Chiang, J.Y., *Regulation of bile acid synthesis.* Front Biosci, 1998. **3**: p. d176-93.
152. Toth, P.P. and M.H. Davidson, *High-density lipoproteins: marker of cardiovascular risk and therapeutic target.* J Clin Lipidol, 2010. **4**(5): p. 359-64.
153. Kris-Etherton, P.M., et al., *The effect of diet on plasma lipids, lipoproteins, and coronary heart disease.* J Am Diet Assoc, 1988. **88**(11): p. 1373-400.
154. Potter, J.D., *Colon cancer--do the nutritional epidemiology, the gut physiology and the molecular biology tell the same story?* J Nutr, 1993. **123**(2 Suppl): p. 418-23.
155. McKeown-Eyssen, G., *Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk?* Cancer Epidemiol Biomarkers Prev, 1994. **3**(8): p. 687-95.
156. Devroey, D., et al., *Serum lipid comparison in patients treated by statins or fibrates: existence of bad HDL-C responders to statins.* Acta Cardiol, 2003. **58**(3): p. 179-84.
157. Fraser, G.E., *Vegetarian diets: what do we know of their effects on common chronic diseases?* Am J Clin Nutr, 2009. **89**(5): p. 1607S-1612S.
158. Lieberman, D.A., et al., *Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals.* JAMA, 2003. **290**(22): p. 2959-67.
159. Ravasco, P., et al., *Nutritional risks and colorectal cancer in a Portuguese population.* Nutr Hosp, 2005. **20**(3): p. 165-72.
160. Haggar, F.A. and R.P. Boushey, *Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors.* Clin Colon Rectal Surg, 2009. **22**(4): p. 191-7.
161. Toriola, A.T., et al., *Alcohol consumption and risk of colorectal cancer: the Findrink study.* Eur J Epidemiol, 2008. **23**(6): p. 395-401.

162. Cleary, S.P., et al., *Cigarette smoking, genetic variants in carcinogen-metabolizing enzymes, and colorectal cancer risk.* Am J Epidemiol, 2010. **172**(9): p. 1000-14.
163. Potter JD. Bigler J, F.L., et al., *Colorectal adenomatous and hyperplastic polyps: smoking and N-acetyltransferase 2 polymorphisms. Cancer Epidemiology Biomarkers Prev.*, 1999. **8**(1): p. 69-75.
164. O'Brien MJ, W.S., Zauber AG, et al., *The National Polyp Study: patient and polyp characteristics associated with high-grade displasia in colorectal adenomas.* Gastroenterology, 1990. **98**(2): p. 371-379.
165. Lim, Y.J., et al., *Increased pulse wave velocity reflecting arterial stiffness in patients with colorectal adenomas.* J Clin Biochem Nutr, 2010. **47**(3): p. 261-5.
166. Siri-Tarino, P.W., et al., *Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients.* Curr Atheroscler Rep, 2010. **12**(6): p. 384-90.
167. Siri-Tarino, P.W., et al., *Saturated fat, carbohydrate, and cardiovascular disease.* Am J Clin Nutr, 2010. **91**(3): p. 502-9.
168. Mensink, R.P., et al., *Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials.* Am J Clin Nutr, 2003. **77**(5): p. 1146-55.
169. Jemal, A., et al., *Global cancer statistics.* CA Cancer J Clin, 2011. **61**(2): p. 69-90.

TABLES

TABLE 1. Selected Characteristics of Cases and Controls in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Characteristics*	Adenoma Cases (N=534)	Colonoscopy-Negative Controls (N=644)	P+
Demographics			
Age (yrs)	58.2 (9.7)	52.9(10.9)	<0.0001
Male (%)	61.8	37.6	<0.0001
White race (%)	97.9	97.1	0.27
Family History			
1° Relative with colon cancer (%)	19.9	33.1	<0.0001
Body size/lifestyle			
Waist to hip ratio	0.93 (0.14)	0.88 (0.11)	<0.0001
Body mass index (kg/m^2)	27.3 (4.7)	26.9 (5.0)	0.10
Physical activity (MET hours/day)	36.8 (38.9)	32.8 (30.5)	0.50
Total alcohol (g/day)	10.1 (16.5)	6.5 (13.5)	<0.0001
Pack-years of cigarettes smoked[a]	19.3 (23.3)	13.1 (22.1)	0.002
HRT user among women (%)	38.6	49.5	0.03
Regularly take an NSAID[b] (%)	12.2	20.2	0.0002
Dietary intakes			
Total energy intake (kcal/day)	2,091.8 (774.8)	2,007.3 (715.8)	0.08
Total fat (g/day)	73.4 (34.2)	68.4 (30.2)	0.02
Saturated fat (g/day)	25.3 (12.8)	23.8 (11.5)	0.05
Monounsaturated fat (g/day)	27.9 (13.6)	25.8 (11.9)	0.02
Polyunsaturated fat (g/day)	13.4 (6.4)	12.5 (5.5)	0.04
Total calcium (mg/day)	956.6 (524.3)	978.3 (518.6)	0.37
$25(OH)D_3$ concentration (ng/mL)	23.8 (9.7)	24.7 (10.6)	0.16
Red and processed meats (serving/day)	7.4 (6.2)	6.5 (5.0)	0.20
Dietary fiber (g/day)	19.6 (8.7)	19.4 (8.8)	0.71
Lipids			
Total cholesterol (mg/dl)	220.7 (42.5)	217.5 (42.3)	0.20
High-density lipoprotein cholesterol (mg/dl)	42.4 (13.5)	45.6 (14.6)	0.0001
Low-density lipoprotein cholesterol (mg/dl)	150.8 (39.8)	145.4 (38.5)	0.02

TABLE 1. Selected Characteristics of Cases and Controls in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Characteristics*	Adenoma Cases (N=534)	Colonoscopy-Negative Controls (N=644)	P+
Very-low-density lipoprotein cholesterol (mg/dl)	26.5 (15.4)	25.3 (14.6)	0.12
Triglycerides (mg/dl)	144.5 (114.1)	136.0 (95.8)	0.14

Abbreviations: MET, metabolic equivalent task; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; 25(OH)D_3, 25-hydroxy-vitamin D_3.

*Continuous variables presented as mean (standard deviation); categorical variables presented as proportions in percent.

+For continuous variables, statistical analysis is based on t-test. For categorical variables, the statistical analysis is based on chi-square test.

[a] Includes non- and ex-smokers.

[b] At least once a week.

Table 2. Crude Associations of Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristic and Quartile of Lipid	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All colorectal adenoma										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.24	0.90, 1.72	1.04	0.76, 1.41	1.46	1.05, 2.04	0.93	0.66, 1.29	1.12	0.81, 1.56
3	1.15	0.82, 1.59	0.74	0.54, 1.02	1.29	0.92, 1.81	1.11	0.81, 1.53	1.19	0.86, 1.66
4	1.15	0.83, 1.60	0.57	0.41, 0.80	1.46	1.04, 2.04	1.14	0.83, 1.57	1.25	0.90, 1.73
P_{trend}[a]	*0.54*		*0.0002*		*0.07*		*0.28*		*0.21*	
Location										
Right colon[b]										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.35	0.82, 2.24	0.86	0.55, 1.33	1.53	0.92, 2.54	1.28	0.73, 2.24	1.38	0.78, 2.47
3	1.44	0.87, 2.38	0.47	0.28, 0.78	1.32	0.78, 2.25	1.70	1.01, 2.86	2.05	1.19, 3.54
4	1.24	0.74, 2.08	0.48	0.29, 0.80	1.29	0.76, 2.19	2.13	1.28, 3.53	2.49	1.47, 4.24
P_{trend}[a]	*0.43*		*0.001*		*0.51*		*0.002*		*0.0003*	
Left colon[c]										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.21	0.86, 1.70	1.10	0.79, 1.51	1.46	1.03, 2.07	0.88	0.62, 1.24	1.10	0.78, 1.54
3	1.1	0.78, 1.56	0.77	0.55, 1.07	1.26	0.88, 1.81	1.00	0.71, 1.39	1.04	0.73, 1.46
4	1.13	0.80, 1.59	0.58	0.41, 0.83	1.48	1.04, 2.10	1.03	0.74, 1.44	1.13	0.80, 1.59
P_{trend}[a]	*0.64*		*0.001*		*0.07*		*0.64*		*0.56*	
Multiplicity										
Multiple adenomas										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.13	0.70, 1.83	1.06	0.68, 1.66	1.45	0.89, 2.37	0.97	0.59, 1.60	1.13	0.69, 1.86
3	1.05	0.65, 1.71	0.75	0.46, 1.20	1.17	0.70, 1.97	0.93	0.57, 1.52	1.03	0.62, 1.71
4	0.97	0.59, 1.59	0.55	0.33, 0.94	1.24	0.74, 2.07	1.18	0.73, 1.88	1.40	0.86, 2.26
P_{trend}[a]	*0.82*		*0.01*		*0.62*		*0.45*		*0.17*	

Table 2. Crude Associations of Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristic and Quartile of Lipid	Total Cholesterol		HDL Cholesterol		LDL Cholesterol		VLDL Cholesterol		Triglycerides	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Single adenoma										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.30	0.90, 1.86	1.03	0.73, 1.45	1.47	1.01, 2.14	0.90	0.62, 1.32	1.12	0.77, 1.61
3	1.19	0.82, 1.73	0.74	0.52, 1.06	1.35	0.92, 1.98	1.20	0.84, 1.70	1.26	0.88, 1.82
4	1.24	0.86, 1.79	0.58	0.40, 0.85	1.56	1.07, 2.28	1.12	0.79, 1.61	1.18	0.82, 1.70
P_{trend}[a]	*0.36*		*0.001*		*0.04*		*0.34*		*0.41*	
Size of largest adenoma[d]										
Large adenoma (≥1cm)										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.50	0.94, 2.39	1.00	0.66, 1.53	1.64	1.02, 2.64	1.28	0.79, 2.07	1.38	0.85, 2.23
3	1.25	0.77, 2.03	0.65	0.41, 1.03	1.14	0.68, 1.91	1.13	0.70, 1.83	1.14	0.69, 1.88
4	1.21	0.74, 1.89	0.43	0.25, 0.72	1.45	0.88, 2.37	1.34	0.84, 2.14	1.51	0.94, 2.43
P_{trend}[a]	*0.65*		*0.0003*		*0.35*		*0.32*		*0.16*	
Small adenoma (< 1 cm)										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.06	0.72, 1.57	1.09	0.76, 1.57	1.32	0.88, 1.96	0.91	0.60, 1.37	1.13	0.76, 1.69
3	1.05	0.71, 1.56	0.83	0.57, 1.21	1.22	0.81, 1.84	1.27	0.87, 1.85	1.38	0.93, 2.04
4	1.19	0.81, 1.75	0.66	0.44, 0.98	1.52	1.02, 2.25	1.20	0.82, 1.76	1.27	0.86, 1.89
P_{trend}[a]	*0.39*		*0.02*		*0.06*		*0.20*		*0.23*	
Shape of largest adenoma										
Pedunculated										
1 (ref.)	1.00		1.00		1.00		1		1.00	
2	1.49	0.90, 2.47	1.23	0.76, 1.98	1.84	1.09, 3.10	0.94	0.55, 1.60	1.06	0.62, 1.79
3	0.93	0.53, 1.61	0.84	0.50, 1.39	0.93	0.51, 1.69	0.99	0.60, 1.66	1.06	0.62, 1.80
4	1.05	0.61, 1.72	0.46	0.25, 0.84	1.37	0.78, 2.39	1.03	0.62, 1.73	1.16	0.69, 1.96
P_{trend}[a]	*0.70*		*0.004*		*0.75*		*0.83*		*0.57*	

Table 2. Crude Associations of Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristic and Quartile of Lipid	Total Cholesterol		HDL Cholesterol		LDL Cholesterol		VLDL Cholesterol		Triglycerides	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sessile										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.16	0.77, 1.76	0.97	0.67, 1.41	1.27	0.84, 1.93	0.99	0.65, 1.51	1.14	0.75, 1.73
3	1.27	0.85, 1.92	0.62	0.41, 0.92	1.18	0.77, 1.82	1.23	0.83, 1.84	1.30	0.86, 1.97
4	1.33	0.89, 2.00	0.64	0.43, 0.96	1.64	1.09, 2.47	1.35	0.91, 2.01	1.44	0.96, 2.16
P_{trend}[a]	*0.15*		*0.01*		*0.03*		*0.08*		*0.07*	
Histologic type of largest adenoma										
Villous or tubulovillous										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.29	0.81, 2.07	0.92	0.59, 1.44	1.44	0.89, 2.31	1.34	0.83, 2.15	1.40	0.87, 2.25
3	1.16	0.71, 1.87	0.80	0.51, 1.27	1.08	0.65, 1.79	1.00	0.61, 1.64	1.00	0.60, 1.66
4	1.07	0.66, 1.75	0.57	0.35, 0.95	1.31	0.80, 2.14	1.26	0.79, 2.02	1.31	0.81, 2.11
P_{trend}[a]	*0.92*		*0.02*		*0.50*		*0.56*		*0.53*	
Tubular										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.19	0.83, 1.72	1.12	0.79, 1.57	1.46	1.00, 2.14	0.73	0.50, 1.10	0.96	0.66, 1.40
3	1.14	0.79, 1.65	0.73	0.51, 1.05	1.38	0.93, 2.03	1.15	0.79, 1.61	1.28	0.89, 1.84
4	1.17	0.81, 1.70	0.57	0.39, 0.84	1.54	1.05, 2.26	1.09	0.76, 1.56	1.22	0.84, 1.76
P_{trend}[a]	*0.47*		*0.001*		*0.05*		*0.27*		*0.18*	
Degree of atypia of largest adenoma										
Mild										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.07	0.71, 1.60	1.06	0.72, 1.55	1.44	0.95, 2.18	0.83	0.54, 1.10	1.08	0.71, 1.63
3	1.03	0.68, 1.54	0.72	0.48, 1.08	1.13	0.73, 1.75	1.11	0.79, 1.61	1.27	0.84, 1.91
4	1.08	0.72, 1.62	0.62	0.40, 0.94	1.54	1.01, 2.34	1.00	0.76, 1.56	1.13	0.74, 1.70
P_{trend}[a]	*0.77*		*0.01*		*0.10*		*0.73*		*0.57*	

Table 2. Crude Associations of Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristic and Quartile of Lipid	Total Cholesterol		HDL Cholesterol		LDL Cholesterol		VLDL Cholesterol		Triglycerides	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Moderate/Severe										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.50	0.99, 2.27	1.06	0.72, 1.55	1.52	0.99, 2.32	1.01	0.66, 1.54	1.15	0.76, 1.74
3	1.39	0.91, 2.12	0.79	0.53, 1.17	1.58	1.03, 2.43	1.05	0.70, 1.58	1.04	0.68, 1.60
4	1.29	0.84, 1.98	0.51	0.33, 0.80	1.42	0.92, 2.20	1.32	0.88, 1.96	1.38	0.92, 2.07
P_{trend}[a]	*0.37*		*0.001*		*0.15*		*0.13*		*0.14*	

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; OR, odds ratio; CI, confidence interval.

a P_{trend} values (2-sided) were calculated by including the median of each quartile of lipid level as a continuous variable.

b At least one adenoma in the right colon, which includes the cecum, ascending colon, hepatic flexure, and transverse colon

c At least one adenoma in the left colon, which includes the splenic flexure, descending colon, sigmoid colon, and rectum.

d Adenoma size from in vivo comparison of maximum diameter to fully opened endoscope forceps.

Table 3. Multivariable-Adjusted Associations of Serum Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
All colorectal adenoma										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.99	0.66, 1.50	1.05	0.71, 1.57	1.13	0.74, 1.74	0.70	0.46, 1.08	0.87	0.57, 1.32
3	0.92	0.61, 1.40	1.04	0.67, 1.61	0.93	0.60, 1.44	0.85	0.56, 1.30	0.91	0.59, 1.40
4	0.84	0.55, 1.29	0.77	0.47, 1.27	1.05	0.68, 1.61	0.83	0.54, 1.29	0.95	0.61, 1.47
P_{trend}[b]	*0.38*		*0.30*		*0.95*		*0.72*		*0.99*	
Location										
Right colon[c]										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.97	0.50, 1.90	0.81	0.44, 1.47	0.92	0.47, 1.81	1.06	0.50, 2.24	1.39	0.63, 3.09
3	1.01	0.52, 1.98	0.71	0.35, 1.42	0.76	0.38, 1.50	1.38	0.67, 2.86	1.87	0.86, 4.10
4	0.77	0.38, 1.53	0.59	0.26, 1.35	0.74	0.37, 1.48	1.36	0.65, 2.84	1.94	0.88, 4.27
P_{trend}[b]	*0.46*		*0.20*		*0.33*		*0.37*		*0.12*	
Left colon[d]										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.94	0.61, 1.44	1.13	0.74, 1.71	1.09	0.70, 1.69	0.67	0.43, 1.05	0.84	0.55, 1.30
3	0.94	0.61, 1.45	1.12	0.71, 1.77	0.93	0.59, 1.46	0.81	0.52, 1.25	0.82	0.52, 1.29
4	0.85	0.55, 1.32	0.87	0.52, 1.45	1.11	0.71, 1.72	0.76	0.48, 1.19	0.84	0.53, 1.34
P_{trend}[b]	*0.49*		*0.55*		*0.79*		*0.47*		*0.60*	
Multiplicity										
Multiple adenomas										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.79	0.43, 1.45	1.17	0.65, 2.09	0.99	0.53, 1.86	0.68	0.36, 1.28	0.83	0.44, 1.57
3	0.92	0.50, 1.69	1.47	0.77, 2.79	0.81	0.43, 1.54	0.65	0.34, 1.24	0.71	0.36, 1.39
4	0.68	0.36, 1.28	1.17	0.55, 2.52	0.91	0.48, 1.70	0.60	0.31, 1.16	0.76	0.38, 1.48
P_{trend}[b]	*0.31*		*0.57*		*0.66*		*0.21*		*0.50*	
Single adenoma										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.04	0.66, 1.64	1.00	0.65, 1.55	1.18	0.74, 1.90	0.71	0.44, 1.15	0.88	0.55, 1.40
3	0.96	0.60, 1.53	0.96	0.59, 1.54	1.02	0.63, 1.65	0.96	0.61, 1.52	1.00	0.63, 1.61
4	0.90	0.56, 1.44	0.64	0.37, 1.11	1.13	0.70, 1.83	0.94	0.58, 1.51	1.02	0.63, 1.65
P_{trend}[b]	*0.58*		*0.11*		*0.79*		*0.82*		*0.82*	

Table 3. Multivariable-Adjusted Associations of Serum Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Size of largest adenoma[e]										
≥1 cm										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.20	0.67, 2.14	0.84	0.48, 1.48	1.40	0.77, 2.55	0.89	0.49, 1.64	0.95	0.52, 1.73
3	1.00	0.55, 1.84	0.97	0.53, 1.80	0.80	0.42, 1.53	0.82	0.44, 1.53	0.74	0.39, 1.40
4	0.78	0.42, 1.45	0.62	0.29, 1.31	1.00	0.54, 1.86	0.86	0.46, 1.61	0.94	0.50, 1.77
P_{trend}[b]	*0.32*		*0.28*		*0.58*		*0.70*		*0.92*	
< 1 cm										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.80	0.49, 1.31	1.16	0.72, 1.85	0.91	0.54, 1.51	0.67	0.40, 1.12	0.91	0.55, 1.51
3	0.85	0.52, 1.39	1.14	0.69, 1.90	0.87	0.52, 1.45	0.96	0.58, 1.57	1.11	0.67, 1.86
4	0.88	0.54, 1.43	0.88	0.49, 1.58	1.08	0.66, 1.78	0.83	0.49, 1.40	0.98	0.58, 1.67
P_{trend}[b]	*0.70*		*0.63*		*0.71*		*0.85*		*0.94*	
Shape of largest adenoma										
Pedunculated										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.16	0.62, 2.18	1.28	0.68, 2.40	1.75	0.89, 3.42	0.53	0.27, 1.06	0.63	0.32, 1.24
3	0.78	0.39, 1.55	1.24	0.62, 2.48	0.74	0.35, 1.57	0.63	0.33, 1.23	0.67	0.34, 1.34
4	0.77	0.39, 1.52	0.85	0.37, 1.92	1.10	0.54, 2.23	0.62	0.32, 1.21	0.72	0.37, 1.42
P_{trend}[b]	*0.28*		*0.65*		*0.60*		*0.37*		*0.61*	
Sessile										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.93	0.56, 1.54	0.97	0.60, 1.56	0.96	0.57, 1.62	0.70	0.41, 1.19	0.84	0.50, 1.41
3	1.09	0.66, 1.79	0.86	0.51, 1.47	0.89	0.53, 1.51	0.88	0.53, 1.47	0.93	0.55, 1.57
4	0.93	0.56, 1.56	0.84	0.46, 1.52	1.14	0.68, 1.89	0.92	0.54, 1.57	1.02	0.59, 1.75
P_{trend}[b]	*0.28*		*0.52*		*0.61*		*0.37*		*0.71*	

Table 3. Multivariable-Adjusted Associations of Serum Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Histologic type of largest adenoma										
Villous or tubulovillous										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.90	0.49, 1.64	0.93	0.52, 1.67	1.16	0.63, 2.14	0.85	0.46, 1.57	0.94	0.52, 1.71
3	0.96	0.53, 1.77	1.18	0.63, 2.23	0.82	0.43, 1.55	0.76	0.40, 1.41	0.71	0.37, 1.35
4	0.78	0.42, 1.47	1.07	0.52, 2.19	1.01	0.54, 1.90	0.73	0.39, 1.39	0.77	0.40, 1.46
P_{trend}[b]	*0.50*		*0.74*		*0.78*		*0.37*		*0.39*	
Tubular										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.95	0.60, 1.50	1.15	0.74, 1.78	1.11	0.68, 1.79	0.61	0.37, 1.00	0.79	0.49, 1.27
3	0.94	0.59, 1.50	1.07	0.66, 1.73	0.99	0.61, 1.61	0.86	0.54, 1.37	0.98	0.61, 1.59
4	0.85	0.53, 1.37	0.70	0.40, 1.22	1.10	0.68, 1.77	0.84	0.52, 1.37	1.00	0.61, 1.64
P_{trend}[b]	*0.51*		*0.19*		*0.82*		*0.96*		*0.67*	
Degree of atypia of largest adenoma										
Mild										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.86	0.52, 1.43	1.16	0.72, 1.89	1.10	0.65, 1.87	0.59	0.34, 1.01	0.83	0.49, 1.41
3	0.86	0.51, 1.43	1.21	0.71, 2.06	0.85	0.49, 1.48	0.78	0.47, 1.31	0.90	0.53, 1.55
4	0.77	0.46, 1.30	0.71	0.38, 1.33	1.14	0.67, 1.94	0.70	0.41, 1.19	0.85	0.49, 1.47
P_{trend}[b]	*0.34*		*0.31*		*0.77*		*0.44*		*0.70*	

Table 3. Multivariable-Adjusted Associations of Serum Lipids with Colorectal Adenoma Overall and by Adenoma Characteristics in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Moderate/Severe										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.09	0.65, 1.84	0.99	0.61, 1.63	1.14	0.66, 1.95	0.82	0.48, 1.40	0.90	0.53, 1.52
3	1.14	0.67, 1.94	0.95	0.55, 1.64	1.14	0.67, 1.97	0.87	0.50, 1.49	0.83	0.48, 1.45
4	0.98	0.57, 1.69	0.74	0.39, 1.40	1.06	0.62, 1.84	1.00	0.58, 1.74	1.06	0.61, 1.85
P_{trend}[b]	*0.93*		*0.35*		*0.88*		*0.76*		*0.67*	

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; OR, odds ratio; CI, confidence interval.

[a] Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

[b] P_{trend} values (2-sided) were calculated by including the median of each quartile of lipid level as a continuous variable.

[c] At least one adenoma in the right colon, which includes the cecum, ascending colon, hepatic flexure, and transverse

[d] At least one adenoma in the left colon, which includes the splenic flexure, descending colon, sigmoid colon, and rectum

[e] Adenoma size from *in vivo* comparison of maximum diameter to fully opened endoscope forceps.

Table 4a. Multivariable-Adjusted Stratified Analysis of Serum Lipids with Colorectal Adenoma in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Sex										
Male										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.70	0.40, 1.24	1.06	0.64, 1.75	1.07	0.57, 1.99	1.09	0.59, 2.04	1.21	0.66, 2.25
3	1.00	0.55, 1.84	0.94	0.51, 1.73	0.91	0.47, 1.71	1.13	0.61, 2.09	1.07	0.57, 2.01
4	0.74	0.39, 1.40	0.75	0.33, 1.69	0.98	0.52, 1.84	1.08	0.59, 1.97	1.11	0.60, 2.04
P_{trend}[b]	*0.61*		*0.52*		*0.84*		*0.87*		*0.93*	
Female										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.46	0.80, 2.66	1.25	0.62, 2.52	1.27	0.70, 2.29	0.47	0.26, 0.85	0.65	0.37, 1.15
3	0.88	0.48, 1.64	1.19	0.60, 2.34	1.00	0.53, 1.87	0.69	0.39, 1.23	0.80	0.44, 1.46
4	1.01	0.55, 1.87	0.89	0.44, 1.83	1.24	0.67, 2.29	0.63	0.33, 1.21	0.80	0.42, 1.54
P_{trend}[b]	*0.60*		*0.23*		*0.62*		*0.42*		*0.85*	
Age										
≤ Median										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.07	0.56, 2.05	0.86	0.45, 1.64	1.41	0.72, 2.74	0.71	0.35, 1.43	1.02	0.53, 1.98
3	1.06	0.54, 2.08	0.86	0.42, 1.74	0.88	0.42, 1.83	0.66	0.32, 1.35	0.64	0.29, 1.38
4	0.95	0.45, 1.99	0.75	0.34, 1.65	1.15	0.56, 2.35	0.91	0.44, 1.86	1.21	0.58, 2.51
P_{trend}[b]	*0.96*		*0.46*		*0.90*		*0.98*		*0.51*	
>Median										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.99	0.58, 1.72	1.22	0.73, 2.04	1.05	0.57, 1.87	0.75	0.43, 1.31	0.87	0.50, 1.52
3	0.88	0.50, 1.52	1.18	0.67, 2.07	0.89	0.50, 1.58	1.03	0.60, 1.77	1.11	0.64, 1.93
4	0.82	0.47, 1.41	0.88	0.47, 1.68	0.98	0.55, 1.73	0.93	0.53, 1.62	0.94	0.53, 1.64
P_{trend}[b]	*0.47*		*0.66*		*0.91*		*0.23*		*0.95*	

Table 4a. Multivariable-Adjusted Stratified Analysis of Serum Lipids with Colorectal Adenoma in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Family history										
Without family history										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.03	0.64, 1.65	1.15	0.74, 1.80	1.05	0.64, 1.73	0.65	0.39, 1.07	0.82	0.50, 1.34
3	1.03	0.63, 1.68	1.33	0.81, 2.19	0.93	0.56, 1.53	0.77	0.47, 1.25	0.82	0.50, 1.35
4	0.88	0.54, 1.42	0.92	0.52, 1.63	1.10	0.68, 1.80	0.68	0.41, 1.13	0.78	0.47, 1.31
P_{trend}[b]	*0.57*		*0.87*		*0.78*		*0.32*		*0.46*	
With family history										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.99	0.40, 2.47	0.62	0.23, 1.67	1.36	0.53, 3.50	0.65	0.25, 1.68	0.81	0.32, 2.02
3	0.53	0.21, 1.34	0.51	0.17, 1.47	1.07	0.39, 2.90	0.78	0.30, 2.03	0.85	0.32, 2.26
4	0.78	0.28, 2.19	0.46	0.14, 1.44	0.87	0.30, 2.56	1.07	0.40, 2.86	1.18	0.43, 3.21
P_{trend}[b]	*0.38*		*0.24*		*0.63*		*0.75*		*0.67*	
NSAID use										
<Once/week										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.99	0.63, 1.55	0.87	0.57, 1.35	1.17	0.73, 1.87	0.57	0.36, 0.91	0.69	0.44, 1.08
3	0.81	0.51, 1.28	0.97	0.60, 1.57	0.92	0.57, 1.48	0.72	0.46, 1.14	0.75	0.47, 1.21
4	0.77	0.48, 1.24	0.69	0.40, 1.19	1.01	0.63, 1.62	0.69	0.43, 1.12	0.79	0.48, 1.29
P_{trend}	*0.21*		*0.25*		*0.79*		*0.38*		*0.64*	

Table 4a. Multivariable-Adjusted Stratified Analysis of Serum Lipids with Colorectal Adenoma in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
≥Once/week										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.12	0.47, 2.66	2.50	1.08, 5.81	0.78	0.32, 1.90	0.95	0.34, 2.70	1.53	0.54, 4.33
3	2.00	0.82, 4.88	1.17	0.47, 2.89	1.81	0.74, 4.41	1.47	0.56, 3.85	1.92	0.71, 5.20
4	1.27	0.50, 3.22	0.62	0.21, 1.89	1.23	0.49, 3.08	1.46	0.57, 3.77	2.01	0.76, 5.35
P_{trend}[b]	*0.38*		*0.33*		*0.34*		*0.39*		*0.24*	

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

[a] Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of aspirin or/and non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

[b] P_{trend} values (2-sided) were calculated by including the median of each quartile of lipid level as a continuous variable and confounders.

¶ p for interaction: Total cholesterol*Sex=0.18, HDL*Sex=0.85, LDL*Sex=0.96, VLDL*Sex=0.16, Triglycerides*Sex=0.36; Total cholesterol*Age=0.75, HDL*Age=0.61, LDL*Age=0.77, VLDL*Age=0.75, Triglycerides*Age=0.40; Total cholesterol*Family history=0.76, HDL*Family history=0.44, LDL*Family history=0.90, VLDL*Family history=0.55, Triglycerides*Family history=0.54; Total cholesterol*NSAID=0.59, HDL*NSAID=0.13, LDL*NSAID=0.89, VLDL*NSAID=0.26, Triglycerides*NSAID=0.13.

APPENDIX

Table 4b. Joint/Combined Associations (ORs) of Total Cholesterol and Total Energy with Risk for Colorectal Adenoma

Total energy (kcal)[a]	Total Cholesterol (mg/dl)							
	1st Quartile	95% CI	2nd Quartile	95% CI	3rd Quartile	95% CI	4th Quartile	95% CI
Low	1.00 (ref)	ref.	0.93	0.46, 1.87	0.60	0.28, 1.30	0.73	0.36, 1.47
Medium	0.67	0.31, 1.44	0.69	0.35, 1.40	0.72	0.37, 1.43	0.52	0.25, 1.08
High	0.54	0.25, 1.14	0.57	0.35, 1.40	0.62	0.30, 1.30	0.55	0.25, 1.22

[a]Total energy: 0 kcal/day <Low≤1654.26 kcal/day; 1654.26 kcal/day<Medium≤ 2205.07 kcal/day; 2205.07 kcal/day<High≤4737.82 kcal/day.
*Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of aspirin or/and non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

Table 4c. Joint/Combined Associations (ORs) of HDL Cholesterol and Total Energy with Risk for Colorectal Adenoma

Total energy (kcal)[a]	HDL Cholesterol (mg/dl)							
	1st Quartile	95% CI	2nd Quartile	95% CI	3rd Quartile	95% CI	4th Quartile	95% CI
Low	1.00 (ref)	ref.	1.65	0.77, 3.53	1.88	0.87, 4.09	1.86	0.81, 4.31
Medium	1.88	0.89, 3.96	1.10	0.51, 2.33	1.20	0.55, 2.61	0.93	0.39, 2.22
High	1.08	0.52, 2.28	1.48	0.68, 3.24	1.16	0.50, 2.70	0.60	0.24, 1.53

[a]Total energy: 0 kcal/day <Low≤1654.26 kcal/day; 1654.26 kcal/day<Medium≤ 2205.07 kcal/day; 2205.07 kcal/day<High≤4737.82 kcal/day.
Abbreviation: HDL=High-density lipoprotein cholesterol.
*Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of aspirin or/and non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous)

Table 4d. Joint/Combined Associations (ORs) of LDL Cholesterol and Total Energy with Risk for Colorectal Adenoma

Total energy (kcal)[a]	LDL Cholesterol (mg/dl)							
	1st Quartile	95% CI	2nd Quartile	95% CI	3rd Quartile	95% CI	4th Quartile	95% CI
Low	1.00 (ref)	ref.	1.02	0.49, 2.12	0.42	0.19, 0.94	0.85	0.41, 1.76
Medium	0.46	0.20, 1.04	0.76	0.37, 1.59	0.68	0.33, 1.40	0.57	0.27, 1.18
High	0.53	0.24, 1.17	0.51	0.24, 1.09	0.64	0.29, 1.39	0.59	0.26, 1.33

[a]Total energy: 0 kcal <Low≤1654.26 kcal; 1654.26 kcal<Medium≤ 2205.07 kcal; 2205.07 kcal<High≤4737.82 kcal.
Abbreviation: LDL=Low-density lipoprotein cholesterol.
*Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of aspirin or/and non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

Table 4e. Joint/Combined Associations (ORs) of VLDL Cholesterol and Total Energy with Risk for Colorectal Adenoma

Total energy (kcal)[a]	VLDL Cholesterol (mg/dl)							
	1st Quartile	95% CI	2nd Quartile	95% CI	3rd Quartile	95% CI	4th Quartile	95% CI
Low	1.00 (ref.)	ref.	0.89	0.43, 1.84	0.73	0.37, 1.45	0.72	0.33, 1.14
Medium	0.70	0.35, 1.42	0.50	0.24, 1.04	0.84	0.42, 1.69	0.60	0.30, 1.22
High	0.74	0.36, 1.54	0.42	0.20, 0.92	0.52	0.24, 1.14	0.66	0.31, 1.38

[a]Total energy: 0 kcal <Low≤1654.26 kcal; 1654.26 kcal<Medium≤ 2205.07 kcal; 2205.07 kcal<High≤4737.82 kcal.
Abbreviation: VLDL=Very-low-density lipoprotein cholesterol.
*Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of aspirin or/and non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

Table 4f. Joint/Combined Associations (ORs) of Triglycerides and Total Energy with Risk for Colorectal Adenoma

Total energy (kcal)[a]	Triglycerides (mg/dl)							
	1st Quartile	95% CI	2nd Quartile	95% CI	3rd Quartile	95% CI	4th Quartile	95% CI
Low	1.00 (ref)	ref.	1.07	0.53, 2.16	0.74	0.37, 1.50	0.79	0.36, 1.73
Medium	0.61	0.29, 1.29	0.66	0.32, 1.34	0.87	0.43, 1.78	0.72	0.35, 1.46
High	0.79	0.37, 1.68	0.47	0.22, 1.00	0.57	0.26, 1.26	0.71	0.34, 1.48

[a]Total energy: 0 kcal <Low≤1654.26 kcal; 1654.26 kcal<Medium≤ 2205.07 kcal; 2205.07 kcal<High≤4737.82 kcal.

*Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of aspirin or/and non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

Table 4g. Joint/Combined Associations (ORs) of Triglycerides, Total Cholesterol, Cholesterol Fractions with Risk for Colorectal Adenoma

	Quartiles of Triglycerides (mg/dl)							
	1		2		3		4	
Quartiles of cholesterol	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Total Cholesterol (mg/dl)								
1	1.00 (ref.)		1.33	0.61, 2.88	1.50	0.63, 3.59	1.37	0.54, 3.50
2	1.27	0.61, 2.64	1.16	0.54, 2.49	1.27	0.58, 2.75	1.22	0.54, 2.76
3	1.36	0.59, 3.15	0.76	0.34, 1.70	0.89	0.41, 1.95	1.68	0.79, 3.57
4	1.92	0.70, 5.29	1.12	0.51, 2.46	1.06	0.50, 2.26	0.78	0.37, 1.65
HDL Cholesterol (mg/dl)								
1	1.00 (ref.)		1.49	0.46, 4.88	1.10	0.36, 3.35	1.35	0.47, 3.87
2	1.19	0.38, 3.79	1.05	0.34, 3.28	1.46	0.48, 4.37	1.82	0.56, 5.89
3	1.36	0.44, 4.18	1.65	0.54, 5.00	1.21	0.36, 4.04	0.94	0.27, 3.26
4	1.65	0.53, 5.13	0.61	0.18, 2.02	0.96	0.28, 3.26	0.51	0.11, 2.36
LDL Cholesterol (mg/dl)								
1	1.00 (ref.)		1.28	0.53, 3.09	1.54	0.57, 4.14	0.79	0.33, 1.88
2	1.32	0.59, 2.95	0.88	0.38, 2.04	0.93	0.41, 2.09	1.97	0.85, 4.57
3	0.99	0.42, 2.32	1.02	0.45, 2.29	0.93	0.41, 2.14	1.01	0.43, 2.41
4	1.56	0.64, 3.80	0.98	0.44, 2.17	1.13	0.51, 2.49	0.94	0.40, 2.23

Table 4g. Joint/Combined Associations (ORs) of Triglycerides, Total Cholesterol, Cholesterol Fractions with Risk for Colorectal Adenoma

	Quartiles of Triglycerides (mg/dl)							
	1		2		3		4	
VLDL Cholesterol (mg/dl)								
1	1.00 (ref.)		2.20	0.74, 6.50	-	-	5.16	0.45, 59.25
2	-	-	0.77	0.50, 1.20	-	-	-	-
3	-	-	1.17	0.35, 3.91	0.92	0.59, 1.43	-	-
4	-	-	-	-	0.48	0.12, 1.96	0.94	0.60, 1.48

Abbreviation: HDL=High-density lipoprotein cholesterol; LDL=Low-density lipoprotein cholesterol; VLDL=Very-low-density lipoprotein.

[a]Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity in hours of metabolic equivalent task.

*p for interactions: Triglycerides*Total cholesterol=0.46, Triglycerides*HDL cholesterol=0.32, Triglycerides*LDL cholesterol=0.56, Triglycerides*VLDL cholesterol=0.79.

Table 5. Multivariable-Adjusted Associations (ORs) of Serum Lipids with Colorectal Adenoma Characteristics; A Case-Case Analysis in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Comparison of Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Multiplicity (Multiple/Single)										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.72	0.40, 1.32	1.15	0.66, 2.02	0.71	0.38, 1.32	1.09	0.58, 2.05	1.12	0.60, 2.09
3	0.80	0.43, 1.46	1.42	0.75, 2.68	0.66	0.35, 1.26	0.72	0.39, 1.33	0.77	0.40, 1.47
4	0.70	0.37, 1.32	1.57	0.73, 3.38	0.65	0.34, 1.22	0.81	0.44, 1.49	0.97	0.51, 1.82
P_{trend}[b]	*0.35*		*0.20*		*0.21*		*0.37*		*0.80*	
Size[c] (≥10 cm/< 10 cm)										
1(ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.46	0.80, 2.67	0.84	0.49, 1.46	1.14	0.61, 2.12	1.53	0.81, 2.88	1.11	0.60, 2.06
3	1.00	0.54, 1.87	0.87	0.47, 1.63	0.63	0.32, 1.22	1.00	0.54, 1.85	0.79	0.41, 1.52
4	0.88	0.46, 1.68	0.75	0.35, 1.63	0.75	0.39, 1.42	1.15	0.62, 2.15	1.06	0.56, 2.00
P_{trend}[b]	*0.41*		*0.50*		*0.17*		*1.00*		*0.92*	
Shape of largest adenoma (Sessile/Pedunculated)										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	0.81	0.41, 1.59	0.62	0.32, 1.17	0.61	0.30, 1.23	1.43	0.69, 2.98	1.44	0.70, 2.95
3	1.64	0.80, 3.36	0.58	0.28, 1.23	1.36	0.62, 3.00	1.62	0.82, 3.23	1.53	0.75, 3.14
4	1.32	0.64, 2.72	0.77	0.32, 1.86	1.23	0.59, 2.58	1.81	0.90, 3.61	1.70	0.83, 3.48
P_{trend}[b]	*0.20*		*0.54*		*0.19*		*0.13*		*0.21*	
Histologic type of largest adenoma (Villous or tubulovillous/tubular)										
1 (ref.)	1.00		1.00		1.00		1.00		1.00	
2	1.03	0.57, 1.88	0.85	0.48, 1.50	1.07	0.58, 1.98	1.52	0.81, 2.85	1.21	0.66, 2.24
3	0.95	0.52, 1.76	1.05	0.56, 1.98	0.71	0.37, 1.37	0.91	0.49, 1.69	0.76	0.40, 1.45
4	0.86	0.46, 1.62	1.60	0.76, 3.38	0.77	0.41, 1.45	0.96	0.52, 1.77	0.83	0.44, 1.56
P_{trend}[b]	*0.59*		*0.20*		*0.25*		*0.52*		*0.35*	

Table 5. Multivariable-Adjusted Associations (ORs) of Serum Lipids with Colorectal Adenoma Characteristics; A Case-Case Analysis in the Cancer Prevention Research Unit Case-Control Study, Minnesota, United States, 1991-1994

Comparison of Adenoma Characteristics and Quartiles of Lipids	Total cholesterol		HDL cholesterol		LDL cholesterol		VLDL cholesterol		Triglycerides	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Degree of atypia of largest adenoma (moderate or severe/mild)										
1	1.00		1.00		1.00		1.00		1.00	
2	1.27	0.71, 2.27	0.88	0.52, 1.49	1.01	0.55, 1.85	1.48	0.80, 2.72	1.07	0.59, 1.94
3	1.28	0.71, 2.31	0.84	0.46, 1.53	1.28	0.69, 2.39	1.21	0.68, 2.17	1.00	0.54, 1.85
4	1.20	0.66, 2.21	1.06	0.51, 2.19	0.86	0.47, 1.59	1.43	0.80, 2.56	1.19	0.65, 2.18
P_{trend}[b]	*0.61*		*0.96*		*0.69*		*0.37*		*0.56*	

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; OR, odds ratio; CI, confidence interval.

[a] Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, body mass index (continuous), family history of colorectal cancer in a first-degree relative, hormone replacement therapy, regular use of non-steroidal anti-inflammatory drugs, pack-years of smoking (continuous), alcohol consumption (continuous), physical activity (continuous), total energy (continuous), saturated fat (continuous), polyunsaturated fat (continuous), total red and processed meat intake (continuous).

[b] P_{trend} values (2-sided) were calculated by including the median of each quartile of lipid level as a continuous variable.

[c] Adenoma size from *in vivo* comparison of maximum diameter to fully opened endoscope forceps.