Published in final edited form as:

Cancer Causes Control. 2015 April ; 26(4): 635–643. doi:10.1007/s10552-015-0555-y.

Plasma Lipid Levels and Colorectal Adenoma Risk

John-Anthony Coppola, Martha J. Shrubsole, Qiuyin Cai, Walter E. Smalley, Qi Dai, Reid M. Ness, Sergio Fazio, Wei Zheng, and Harvey J. Murff

Florida State University College of Medicine (JAC); Division of General Internal Medicine and Public Health, Vanderbilt University School of Medicine, Nashville TN (HJM); GRECC, Department of Veterans Affairs, Tennessee Valley Healthcare System, Nashville TN (MJS, QD, WZ; HJM); Division of Epidemiology, Vanderbilt University School of Medicine (MJS, QC, QD, WZ); Department of Preventive Medicine, Vanderbilt University School of Medicine (WES); Division of Gastroenterology, Vanderbilt University School of Medicine (WES, RMN); Center for Preventive Cardiology of the Knight Cardiovascular Institute, Oregon Health & Science University (SF); Vanderbilt Ingram Cancer Center (MJS, QC, QD, WZ, HJM)

Abstract

Purpose—Abnormalities in lipid levels have been associated with colorectal neoplasm risk; however, few studies have adjusted for use of cholesterol-lowering medications. The objective of this study was to determine the association of plasma lipid levels with adenoma risk while accounting for statin medication use.

Methods—We included 254 subjects with advanced adenoma, 246 with single small adenoma, 179 with multiple small adenoma cases, and 403 controls participants in the Tennessee Colorectal Polyp Study who also had plasma lipid measurements performed. Data on the use of statin medications was available for 83.4% of these participants. The association between plasma lipids and adenoma risk was evaluated using logistic regression models.

Results—Participants in the highest quartile of HDL cholesterol (range 52 – 106 mg/dl) had an adjusted odds ratio of 0.49 (95% CI 0.23, 1.07), 0.35 (95% CI 0.13, 0.91) and 0.22 (95% CI 0.09, 0.54) for single small, multiple small, and advanced adenomas compared to the lowest quartile (range 12 – 34 mg/dl), respectively. Participants with the highest quartile of triglyceride levels (range 178 – 721 mg/dl) had an adjusted odds ratio of 2.40 (95% CI 1.26, 4.55), 1.67 (95% CI 0.66, 4.23) and 2.79 (95% CI 1.25, 6.23) for single small, multiple small, and advanced adenoma, respectively compared to the lowest quartile (range 40 – 84 mg/dl). When restricted to individuals with known statin medication use adjusting for statin use did not appreciably affect these results.

Conclusions—We found a direct association between triglyceride plasma levels and an inverse association between plasma HDL cholesterol levels and adenoma risk. Both effects were not appreciably changed when accounting for the regular use of statin medication.

Corresponding author: Harvey J. Murff, M.D., M.P.H., Division of General Internal Medicine and Public Health, Vanderbilt University, 6012 Medical Center East, 1215 21st Avenue South, Nashville, TN 37232-8300, Work: 615 936-8319, Fax: 615 936-1269, harvey.j.murff@vanderbilt.edu.

Conflict of Interest

The authors declare that they have no conflict of interest

Keywords

Neoplasms; Colorectal; Hypolipidemic Agents; Lipoproteins

Introduction

Diabetes mellitus and the metabolic syndrome are increasingly being recognized as risk factors for colorectal cancer [1,2]. A prominent component of these metabolic abnormalities is dyslipidemia, defined as fasting triglycerides (TG) ≥ 150 mg/dl and high-density lipoprotein (HDL) <50 mg/dl (<40 mg/dl in men) [3]. Several prior studies have suggested that abnormalities in circulating lipid levels are associated with colorectal neoplasm risk [4–11]. Although there have been inconsistencies, multiple studies have reported a direct correlation between triglycerides and risk of colorectal adenomas [4,5,7,10,12,13]. Fewer studies exist which have examined other lipid fractions and their results have been mixed. Circulating low-density lipoproteins (LDL) have been reported as directly correlated [7,11] or not correlated [10] with adenoma risk. Elevated HDL cholesterol levels have also been found to be associated with an increased [4,7], decreased [11,14] or no risk [5,15] for colorectal neoplasm. These prior studies could be confounded by medication use as many individuals with dyslipidemia are treated with HMG-CoA reductase inhibitors (statins), which might also have a direct impact on colorectal cancer risk [16]. The first statin medication was approved for sale in the United States in 1991, thus studies published prior or around this date would not have needed to account for statin medication use; nevertheless, most studies investigating lipid fractions and colorectal adenoma risk have been published since the introduction of statin medications. To the best of our knowledge, no prior study has investigated the association of plasma lipids and adenoma risk after adjustment for use of statin medication.

Dyslipidemia could promote colorectal carcinogenesis through several mechanisms [17]. The metabolic pattern of increased triglycerides and reduced HDL cholesterol is also associated with insulin resistance and increased circulating insulin/insulin-like growth factor-1 is associated with colorectal cancer risk [18]. Furthermore, increased LDL cholesterol could be associated with increases in oxidative stress, which in turn might promote neoplastic growth [19,20]. Additionally triglycerides impact bile acid secretion and may influence colorectal cancer risk through this mechanism [21], and most of the biliary cholesterol derives from circulating HDL [22,23].

In this study, we investigated the association of plasma lipids with adenoma risk in a case-control study including 679 adenoma cases and 403 polyp-free controls. We collected detailed drug use information on a subset of this population to determine how use of statins might influence any associations.

Materials and Methods

Participants

Participants were part of the Tennessee Colorectal Polyp Study, an on-going colonoscopy-based case-control study being conducted in Nashville, Tennessee, United States. Study methods have been published elsewhere [24]. Briefly, eligible participants, aged between 40 and 75 years old, were identified from patients scheduled for colonoscopy at the Vanderbilt Gastroenterology Clinic between February 1, 2003 and October 29, 2010 and the Veterans' Affairs Tennessee Valley Health System Nashville campus between August 21, 2003 and May 30, 2007. Potential participants who had a genetic colorectal cancer syndrome (*e. g.* hereditary non-polyposis colorectal cancer or familial adenomatous polyposis) or a prior history of inflammatory bowel disease, adenoma, or any cancer other than non-melanoma skin cancers were excluded. Among 12,585 eligible individuals, 7,621 provided a written informed consent and participated in at least one component of the study (61%). Seventy-six percent of participants ($n = 5824$) participants provided a blood sample and of these plasma lipid levels were measured on 1318 participants (22.6%). The study was approved by the Vanderbilt University Institutional Review Board, the Veterans' Affairs Institutional Review Board, and the Veterans' Affairs Research and Development Committee.

For the current study we utilized case-control sets that had been previously identified as part of a study investigating urinary prostaglandin E_2 metabolite levels and adenoma risk [25]. Cases were classified into three case groups: single small adenomas ($n=248$), multiple small adenomas ($n= 204$) and advanced adenomas ($n= 285$). Controls were matched to case groups by age (within 5 years), gender, race (white/non-white). Additional matching criteria included at least one of the following criteria: sample collection date (within 90 days or season), study site (academic medical center/VA hospital), and regular use of NSAIDs (current; former or never). Out of 1163 potentially eligible participants in this subset, we excluded 81 participants with missing smoking or alcohol use data. The current analyses included 246 single small adenomas, 179 multiple small adenomas, and 254 advanced adenoma cases and 403 polyp-free controls. The initial baseline study questionnaire did not capture information related to statin use and this question was added in June 2004. Of the 1082 participants included in this analysis 83.4% (902) had data on statin medication use.

Outcome assessment

Patient colonoscopy results were recorded using standardized data-entry forms. Information on the number, location, and size of polyps were collected. Polyps were classified as an adenoma (which included villous, tubulovillous, tubular, sessile serrated, and traditional serrated on the basis of a histologic review), hyperplastic, mixed, or other. We additionally characterized cases as having a single small adenoma (< 1 cm), multiple (2 or more) small adenomas, and advanced adenomas. A polyp was considered an advanced adenoma if it met one of the following 3 criteria: 1) size ≥ 1.0 cm, 2) a $>25\%$ villous component, or 3) contained a high-grade dysplasia.

Exposure assessment

A standardized telephone interview was conducted by trained interviewers following colonoscopy to obtain information on medication use, demographics, personal medical history, family history, reproductive history, anthropometry, and lifestyle. Participants completed a semi-quantitative 108-item food frequency questionnaire (FFQ) which was developed to capture diet in the Southeastern United States [26]. Seventy-eight percent (n = 5,906) of all study participants completed the FFQ.

Laboratory assays

Participants recruited prior to colonoscopy were asked to donate a 20 mL fasting blood sample. The blood was drawn into EDTA-containing, ACD-containing, and serum BD Vacutainer® tubes. EDTA tube blood was separated into plasma, buffy coats (white cells), and red blood cells. Samples were processed within 6 hours of collection and stored for future analyses in -80°C freezer. Plasma samples from EDTA tube were used in this study. The levels of lipid biomarkers were measured by using the ACE Alera® Clinical Chemistry System (Alfa Wassermann, Inc, West Caldwell, NJ). The levels of triglycerides, total cholesterol, and HDL-cholesterol, were assayed using the ACE® Triglycerides Reagent (SA1023), Cholesterol Reagent (SA1010), and HDL-C Reagent (SA2038) (Alfa Wassermann, Inc, West Caldwell, NJ), respectively, following the manufacturer's protocols. LDL-cholesterol level was calculated with the Friedwald equation[27] ($[\text{LDL-cholesterol}] = [\text{Total cholesterol}] - [\text{HDL-cholesterol}] - ([\text{triglycerides}]/5)$). In subjects with triglyceride levels above 400 mg/dL, the LDL-cholesterol levels were measured directly using ACE® LDL-C Reagent (SA1040). The level of Lipoprotein(a) was measured using Lipoprotein(a) Reagent Set from Pointe Scientific, Inc (Canton, MI) following the manufacturer's protocols.

Statistical analysis

We compared differences between case and control participants by using Wilcoxon Rank-Sum test for continuous variables or the Cochran-Mantel-Haenszel chi-square test for categorical variables. Conditional logistic regression models were used to estimate risk of colorectal polyps associated with plasma cholesterol levels. Plasma lipids levels were categorized into quartiles on the basis of the distribution of the polyp-free control participants. All models were adjusted for age (continuous), body mass index kg/m^2 (continuous), regular alcohol use (current use, former use, or never used), cigarette use (current use, former use, or never used), regular physical activity in the past 10 years (yes or no), use of hormone replacement therapy (ever, never, or women only), indication for colonoscopy (screening or diagnostic), regular use of NSAIDs or aspirin (yes or no) and study site (Vanderbilt or VA). We constructed similar models restricting to individuals with statin medication information. We categorized statin users as either current users (n = 327) or never users/former users (n = 575). We calculated tests for trend by rank ordering exposure categories and including the variable within the model as a continuous term. We constructed separate logistic regression models with a dependent variable of non-advanced adenoma or advanced adenoma in comparison to controls. All statistical calculations were performed with SAS software (version 9.2; SAS Institute).

Results

The demographic and lifestyle data of the study participants are presented in Table 1. Single small, multiple small, and advanced adenoma cases were older than controls (p value < 0.0001), more likely to have a greater BMI (p value = 0.003), more likely to use tobacco (p value < 0.0001) and alcohol (p value = 0.02). Controls were less likely to report using statin medications (p value = 0.02).

For both men and women there were no statistically significant differences seen between cases and controls for total cholesterol or LDL cholesterol (Table 2). For both men and women, HDL cholesterol was higher in controls (p value < 0.0001 and 0.002 for men and women respectively) and triglycerides lower in controls (p value = 0.005 and 0.003 for men and women respectively) compared to cases. Lipoprotein (a) was higher in controls compared to cases for men (p value = 0.009) only.

We found no association between total cholesterol, LDL cholesterol or lipoprotein (a) and single small, multiple small or advanced adenomas (Table 3). Increasing levels of HDL cholesterol were associated with a reduced risk of single small, multiple small, and advanced adenomas (p_{trend} = 0.06, 0.02, 0.0005 respectively). Participants in the highest quartile of HDL cholesterol had an adjusted odds ratio of 0.22 (95% CI 0.09, 0.54) for an association with advanced adenoma risk compared to individuals in the lowest HDL quartile. Because HDL and triglyceride levels are inversely correlated we also constructed similar models adjusting for triglyceride levels. These results were not substantially altered when mutually adjusting for triglycerides and HDL (data not shown). There was a statistically significant trend for increasing levels of triglycerides associated with increased risks of single small adenomas (p_{trend} = 0.005) compared to controls. This trend remained significant when additionally adjusting for HDL levels. For advanced adenomas, participants in the highest quartile of triglycerides had an adjusted odds ratio of 2.79 (95% CI 1.25, 6.23) for an association with advanced adenoma risk compared to individuals in the lowest triglyceride quartile.

To evaluate the accuracy of self-reported statin medication use, we compared LDL cholesterol levels between statin users (n = 327) and former or never statin users (n =575). The median level of LDL was 96 mg/dl (IQR 76, 120) in statin users and 125 mg/dl (IQR 104, 148) in non-statin users (p < 0.0001). When restricted to participants with information related to statin use and adjusted for statin medication use, there remained a trend towards a reduced association between HDL cholesterol levels and all adenoma types, which was statistically significant only for advanced adenomas (p_{trend} = 0.0007) (Table 4) When restricted participants with information related to statin uses, increasing LDL levels were associated with an increased risk for single small adenomas but this effect was only seen in the middle quartiles (OR_{Q2 versus Q1} 1.94 (95% CI 1.01, 3.73) and OR_{Q3 versus Q1} 1.82 (95% CI 1.01, 3.27). These results remained similar when restricting our analyses to statin users but not adjusting for statin use within the model (data not shown). We found no evidence of an interaction between statin use, lipid level, and adenoma risk for any of the lipid fractions.

Discussion

In this case-control study of colon adenomas we found that higher levels of HDL cholesterol are associated with a reduced risk of multiple small and advanced adenomas and that this association is maintained after adjusting for statin use. Although the effect sizes suggested an inverse association between single small adenomas and HDL cholesterol levels, the trends were only of borderline statistical significance. We found that higher levels of triglycerides were associated with an increased risk of single small and advanced adenomas. This effect was less pronounced for multiple small adenoma cases.

Our results confirm prior studies that have described an association between certain plasma lipids and colorectal neoplasm risk. Liu et al. analyzed individuals who were diagnosed with metabolic syndrome based on the American Heart Association and National Heart Lung Blood Institute and found that men had a stronger correlation with metabolic syndrome and colorectal adenomas, and that only central obesity, low HDL, and high triglycerides were independently associated with colorectal adenomas [14]. Van Duijnhoven et al. reported an inverse association between HDL cholesterol and colon cancer [6]. In contrast to our study, plasma triglycerides were not statistically significantly associated with colon cancer. Otani et al showed there was a correlation between elevated triglycerides and colorectal adenoma which was more pronounced in men than women [13]. In a study including 1,771 adenoma cases and 4,667 controls participants, plasma triglycerides greater than or equal to 150 mg/dL was associated with an odds ratio of 1.47 (95% CI 1.06, 2.04) for advanced adenomas (n = 186) compared to participants with triglycerides less than 150 mg/dL [5]. Bird et al. also reported higher triglyceride levels to be associated with adenoma risk [4].

We found no association between total cholesterol or LDL cholesterol in our primary analysis. We did find a positive association between increasing LDL cholesterol and single small adenoma risk; however, the effect was only found in the middle quartiles and only when our analysis was restricted to individuals with data on statin use. These findings are in contrast to some prior studies that have reported positive associations; however, other studies have not reported any association [6,10]. We found a very strong inverse association between HDL cholesterol and adenoma risk. Prior studies investigating HDL cholesterol have found inverse associations [6,11], null associations [5,15], and positive associations [4,7]. It is not clear why these findings have been so inconsistent with respects to HDL cholesterol. This may be related to study design, study population, and/or choice of outcome (adenoma versus colorectal cancer). With regard to adenoma risk, a cross-sectional study conducted in Korea found that increasing HDL levels correlated with increased prevalence of non-advanced adenomas, but no association was found with advanced adenomas [7]. A case-control study also conducted in Korea reported a non-significant trend for increasing adenoma risk with increasing HDL cholesterol levels [10]. A second cross-sectional study conducted in Germany found a decrease risk of colon adenomas with increased HDL cholesterol levels [11]. In our study we demonstrated a very strong inverse association between HDL cholesterol and adenoma risk. These inconsistencies are challenging to address given the lack of mechanistic insights into how HDL may influence colorectal adenoma risk. However, one can speculate that the HDL connection with colon cancer may work both ways, with the inflammatory state caused by cancer as a depressing force for

plasma HDL levels [28], and the loss of anti-oxidant activity caused by low HDL states as a facilitating force for cancer development [29]. It would be interesting to study whether loss of HDL function without reductions in HDL levels, seen in subjects with end-stage renal disease [30], is also associated with colon cancer. Interestingly, an increased risk of colorectal cancer in subjects with CKD was recently reported [31]. The strength of the inverse association between HDL and cancer in general is given by a recent meta-analysis of several controlled studies [32].

Strengths of the study include detailed information on statin use and a relatively large sample of advanced adenomas. In addition all study participants underwent complete colonoscopy examination. There are several limitations to the study. We were missing information on several important confounders such as personal history of diabetes mellitus, hypertension and concomitant medication use. Second, although the dietary questionnaire was tailored for populations in the Southeast United States, certain food combinations or preparations that are commonly consumed might have been unaccounted for. Another limitation was the lack of data on the duration of statin use. Studies of NSAID use and colorectal neoplasm risk have suggested that duration of use is an important factor to consider when investigating protective associations [33]. In addition, statin use was self-reported, however, we found that those reporting using statin medications did have lower LDL cholesterol levels which would suggest these participants were likely using the medications.

Conclusion

In conclusion, we found a direct association between triglyceride plasma levels and an inverse correlation between plasma HDL cholesterol levels and adenoma risk. Both effects appeared stronger in patients with advanced adenoma compared to those with single and multiple simple adenomas. These findings remained significant after adjustment for statin medication use.

Acknowledgments

We thank Regina Courtney and Jie Wu for their excellent laboratory assistant, and Kimberly Campbell for lipid assays. This study was supported through the National Institute of Health grants P50CA 95103, R01CA97386, R01CA143288, and R01HL106845. Surveys and sample collection, processing, and preparation for this study were conducted by the Survey and Biospecimen Shared Resource, which is supported in part by P30CA068485. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. A portion of this material is the result of work supported with resources and the use of facilities at the VA Tennessee Valley Healthcare System.

References

1. Wu L, Yu C, Jiang H, Tang J, Huang HL, Gao J, Zhang X. Diabetes mellitus and the occurrence of colorectal cancer: an updated meta-analysis of cohort studies. *Diabetes Technol Ther.* 2013; 15 (5): 419–427.10.1089/dia.2012.0263 [PubMed: 23540566]
2. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care.* 2012; 35 (11):2402–2411. 35/11/2402 [pii]. 10.2337/dc12-0336 [PubMed: 23093685]

3. Nikolic D, Katsiki N, Montalto G, Isenovic ER, Mikhailidis DP, Rizzo M. Lipoprotein subfractions in metabolic syndrome and obesity: clinical significance and therapeutic approaches. *Nutrients*. 2013; 5 (3):928–948. nu5030928 [pii]. 10.3390/nu5030928 [PubMed: 23507795]
4. Bird CL, Ingles SA, Frankl HD, Lee ER, Longnecker MP, Haile RW. Serum lipids and adenomas of the left colon and rectum. *Cancer Epidemiol Biomarkers Prev*. 1996; 5 (8):607–612. [PubMed: 8824362]
5. Kim BC, Shin A, Hong CW, Sohn DK, Han KS, Ryu KH, Park BJ, Nam JH, Park JW, Chang HJ, Choi HS, Kim J, Oh JH. Association of colorectal adenoma with components of metabolic syndrome. *Cancer Causes Control*. 2012; 23 (5):727–735.10.1007/s10552-012-9942-9 [PubMed: 22450737]
6. van Duijnhoven FJ, Bueno-De-Mesquita HB, Calligaro M, Jenab M, Pischon T, Jansen EH, Frohlich J, Ayyobi A, Overvad K, Toft-Petersen AP, Tjønneland A, Hansen L, Boutron-Ruault MC, Clavel-Chapelon F, Cottet V, Palli D, Tagliabue G, Panico S, Tumino R, Vineis P, Kaaks R, Teucher B, Boeing H, Drogan D, Trichopoulou A, Lagiou P, Dilis V, Peeters PH, Siersema PD, Rodriguez L, Gonzalez CA, Molina-Montes E, Dorronsoro M, Tormo MJ, Barricarte A, Palmqvist R, Hallmans G, Khaw KT, Tsilidis KK, Crowe FL, Chajes V, Fedirko V, Rinaldi S, Norat T, Riboli E. Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Gut*. 2011; 60 (8):1094–1102.10.1136/gut.2010.225011 [PubMed: 21383385]
7. Yang MH, Rampal S, Sung J, Choi YH, Son HJ, Lee JH, Kim YH, Chang DK, Rhee PL, Kim JJ, Rhee JC, Chun HK, Guallar E, Cho J. The association of serum lipids with colorectal adenomas. *Am J Gastroenterol*. 2013; 108 (5):833–841. ajg201364 [pii]. 10.1038/ajg.2013.64 [PubMed: 23545715]
8. Kim JH, Lim YJ, Kim YH, Sung IK, Shim SG, Oh SO, Park SS, Yang S, Son HJ, Rhee PL, Kim JJ, Rhee JC, Choi YH. Is metabolic syndrome a risk factor for colorectal adenoma? *Cancer Epidemiol Biomarkers Prev*. 2007; 16 (8):1543–1546. 16/8/1543 [pii]. 10.1158/1055-9965.EPI-07-0199 [PubMed: 17684126]
9. Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. *Cancer*. 2006; 107 (1):28–36.10.1002/cncr.21950 [PubMed: 16721800]
10. Park SK, Joo JS, Kim DH, Kim YE, Kang D, Yoo KY. Association of serum lipids and glucose with the risk of colorectal adenomatous polyp in men: a case-control study in Korea. *Journal of Korean medical science*. 2000; 15 (6):690–695. [PubMed: 11194196]
11. Bayerdorffer E, Mannes GA, Richter WO, Ochsenkuhn T, Seeholzer G, Kopcke W, Wiebecke B, Paumgartner G. Decreased high-density lipoprotein cholesterol and increased low-density cholesterol levels in patients with colorectal adenomas. *Ann Intern Med*. 1993; 118 (7):481–487. [PubMed: 8442619]
12. Lee GE, Park HS, Yun KE, Jun SH, Kim HK, Cho SI, Kim JH. Association between BMI and metabolic syndrome and adenomatous colonic polyps in Korean men. *Obesity (Silver Spring)*. 2008; 16 (6):1434–1439. oby2008216 [pii]. 10.1038/oby.2008.216 [PubMed: 18388894]
13. Otani T, Iwasaki M, Ikeda S, Kozu T, Saito H, Mutoh M, Wakabayashi K, Tsugane S. Serum triglycerides and colorectal adenoma in a case-control study among cancer screening examinees (Japan). *Cancer Causes Control*. 2006; 17 (10):1245–1252.10.1007/s10552-006-0065-z [PubMed: 17111255]
14. Liu CS, Hsu HS, Li CI, Jan CI, Li TC, Lin WY, Lin T, Chen YC, Lee CC, Lin CC. Central obesity and atherogenic dyslipidemia in metabolic syndrome are associated with increased risk for colorectal adenoma in a Chinese population. *BMC Gastroenterol*. 2010; 10:51.10.1186/1471-230X-10-51 [PubMed: 20507579]
15. Gaard M, Tretli S, Urdal P. Blood lipid and lipoprotein levels and the risk of cancer of the colon and rectum. A prospective study of 62,173 Norwegian men and women. *Scand J Gastroenterol*. 1997; 32 (2):162–168. [PubMed: 9051877]
16. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, Low M, Greenston JK, Rennert G. Statins and the risk of colorectal cancer. *N Engl J Med*. 2005; 352 (21):2184–2192. 352/21/2184 [pii]. 10.1056/NEJMoa043792 [PubMed: 15917383]

17. 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):687–695. [PubMed: 7881343]
18. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr.* 2007; 86 (3):s836–842. [PubMed: 18265477]
19. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? *Am J Pathol.* 2006; 169 (5):1505–1522. S0002-9440(10)62617-X [pii]. 10.2353/ajpath.2006.051090 [PubMed: 17071576]
20. Kim YJ, Kim EH, Hahm KB. Oxidative stress in inflammation-based gastrointestinal tract diseases: challenges and opportunities. *J Gastroenterol Hepatol.* 2012; 27 (6):1004–1010.10.1111/j.1440-1746.2012.07108.x [PubMed: 22413852]
21. Barrasa JI, Olmo N, Lizarbe MA, Turnay J. Bile acids in the colon, from healthy to cytotoxic molecules. *Toxicol In Vitro.* 2013; 27 (2):964–977. S0887-2333(12)00358-X [pii]. 10.1016/j.tiv.2012.12.020 [PubMed: 23274766]
22. Schwartz CC, Halloran LG, Vlahcevic ZR, Gregory DH, Swell L. Preferential utilization of free cholesterol from high-density lipoproteins for biliary cholesterol secretion in man. *Science.* 1978; 200 (4337):62–64. [PubMed: 204996]
23. Robins SJ, Fasulo JM. High density lipoproteins, but not other lipoproteins, provide a vehicle for sterol transport to bile. *J Clin Invest.* 1997; 99 (3):380–384.10.1172/JCI119170 [PubMed: 9022069]
24. Shrubsole MJ, Wu H, Ness RM, Shyr Y, Smalley WE, Zheng W. Alcohol drinking, cigarette smoking, and risk of colorectal adenomatous and hyperplastic polyps. *Am J Epidemiol.* 2008; 167 (9):1050–1058. kwm400 [pii]. 10.1093/aje/kwm400 [PubMed: 18304959]
25. Shrubsole MJ, Cai Q, Wen W, Milne G, Smalley WE, Chen Z, Ness RM, Zheng W. Urinary prostaglandin E2 metabolite and risk for colorectal adenoma. *Cancer Prev Res (Phila).* 2012; 5 (2):336–342.10.1158/1940-6207.CAPR-11-0426 [PubMed: 22166248]
26. Buchowski MS, Schlundt DG, Hargreaves MK, Hankin JH, Signorello LB, Blot WJ. Development of a culturally sensitive food frequency questionnaire for use in the Southern Community Cohort Study. *Cell Mol Biol (Noisy-le-grand).* 2003; 49 (8):1295–1304. [PubMed: 14984001]
27. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972; 18 (6):499–502. [PubMed: 4337382]
28. Westerterp M, Bochem AE, Yvan-Charvet L, Murphy AJ, Wang N, Tall AR. ATP-binding cassette transporters, atherosclerosis, and inflammation. *Circulation research.* 2014; 114 (1):157–170.10.1161/CIRCRESAHA.114.300738 [PubMed: 24385509]
29. Robinson JG. Low high-density lipoprotein cholesterol and chronic disease risk marker or causal? *J Am Coll Cardiol.* 2010; 55 (25):2855–2857.10.1016/j.jacc.2010.01.053 [PubMed: 20579543]
30. Yamamoto S, Yancey PG, Ikizler TA, Jerome WG, Kaseda R, Cox B, Bian A, Shintani A, Fogo AB, Linton MF, Fazio S, Kon V. Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. *J Am Coll Cardiol.* 2012; 60 (23):2372–2379.10.1016/j.jacc.2012.09.013 [PubMed: 23141484]
31. Wu MY, Chang TC, Chao TY, Huang MT, Lin HW. Risk of colorectal cancer in chronic kidney disease: a matched cohort study based on administrative data. *Annals of surgical oncology.* 2013; 20 (12):3885–3891.10.1245/s10434-013-3065-8 [PubMed: 23807660]
32. Jafri H, Alsheikh-Ali AA, Karas RH. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy. *J Am Coll Cardiol.* 2010; 55 (25):2846–2854.10.1016/j.jacc.2009.12.069 [PubMed: 20579542]
33. Ye X, Fu J, Yang Y, Chen S. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. *PLoS One.* 2013; 8 (2):e57578.10.1371/journal.pone.0057578 [PubMed: 23451245]

Table 1

Demographic Characteristics between Cases and Control

Characteristic	Advanced cases (n = 254)	Multiple Small Adenomas (n = 179)	Single Small Adenomas (n = 246)	Controls (n = 403)	p-value ^d
Age, (years, median, IQR)	58.8 (53.4, 64.3)	60.1 (55.0, 65.2)	57.0 (51.7, 62.9)	56.4 (51.3, 62.8)	<0.0001
Sex (%) Female	74 (29.1)	35 (19.6)	67 (27.2)	132 (32.8)	0.09
Race (%)					
Caucasian	224 (88.2)	165 (92.2)	233 (94.7)	348 (86.4)	
African American	23 (9.1)	13 (7.3)	10 (4.1)	47 (11.7)	0.57
Other	7 (2.8)	1 (0.6)	3 (1.2)	8 (2.0)	
Cigarette Smoking (%)					
Current	72 (28.4)	59 (33.0)	42 (17.1)	65 (16.1)	
Former	100 (39.4)	68 (38.0)	98 (39.8)	140 (34.7)	<0.0001
Never	82 (32.3)	52 (29.1)	106 (43.1)	198 (49.1)	
Alcohol consumption (%)					
Current	60 (23.6)	84 (47.0)	69 (28.1)	79 (19.6)	
Former	79 (31.1)	59 (33.0)	53 (21.5)	93 (23.1)	0.02
Never	115 (45.3)	84 (47.0)	124 (50.4)	231 (57.3)	
Regularly exercised (%)	133 (52.4)	75 (41.9)	138 (56.1)	221 (54.8)	0.14
BMI (kg/m ² , median, IQR)	28.1 (24.4, 31.0)	28.2 (25.7, 32.1)	27.9 (24.8, 32.1)	27.2 (23.7, 30.7)	0.003
Use of HRT (ever, %) ^b	45 (60.8)	20 (57.1)	42 (62.7)	72 (54.6)	0.43
Study site (%)					
Veterans Affairs hospital	94 (37.0)	77 (43.0)	75 (30.5)	129 (32.0)	
Academic center	160 (63.0)	102 (57.0.7)	171 (69.5)	274 (68.0)	0.04
Indication for colonoscopy (%)					
Screening	148 (58.3)	102 (57.0)	150 (61.0)	230 (57.1)	0.81
Family History	18 (7.1)	21 (11.7)	31 (12.6)	57 (14.1)	0.77
Diagnostic	74 (29.1)	37 (20.7)	45 (18.3)	77 (19.1)	
Other	14 (5.5)	19 (10.6)	20 (8.1)	39 (9.7)	
NSAID use (%)					
Current	110 (44.0)	97 (54.2)	134 (54.5)	218 (54.4)	0.003
Former	16 (6.4)	16 (8.9)	20 (8.1)	36 (9.0)	

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Characteristic	Advanced cases (n = 254)	Multiple Small Adenomas (n = 179)	Single Small Adenomas (n = 246)	Controls (n = 403)	p-value ^a
Never	124 (49.6)	66 (36.9)	147 (36.5)	147 (36.7)	
Statin use (%) ^c					
Current	77 (30.2)	68 (38.0)	86 (35.0)	96 (23.8)	
Former	3 (1.2)	2 (1.1)	5 (2.0)	5 (1.2)	
Never	124 (48.8)	74 (41.3)	143(58.1)	219 (54.3)	<0.0001
Missing	50 (19.7)	35 (19.6)	12 (4.9)	83 (20.6)	

^a For variables expressed as medians *P* calculated with Wilcoxon Rank-Order Sum test for variables expressed as percentages *P* calculated with χ^2

^b Includes women only (n = 308)

^c Question included in later version of survey (n = 902: 204 advanced adenoma cases, 144 multiple small adenoma cases, 234 single small adenoma cases, and 320 controls)

Table 2

Plasma Lipid Concentrations between Cases and Control

Characteristic	Advanced cases	Multiple Small Adenomas	Single Small Adenomas	Controls	p-value ^c
Men (N)	180	144	179	271	
Total cholesterol ^a	180 (158, 207) ^b	179 (148, 203)	184 (160, 209)	186 (153, 210)	0.35
LDL cholesterol	112 (89, 136)	107 (79, 129)	112 (93, 136)	111 (90, 139)	0.39
HDL cholesterol	35 (31, 41)	35 (30, 40)	38 (32, 44)	38 (32, 46)	<0.0001
Triglycerides	151 (109, 206)	151 (109, 191)	149 (101, 215)	130 (88, 190)	0.005
Lipoprotein(a)	13.4 (5.5, 33.6)	12.7 (4.8, 29.2)	13.6 (5.7, 30.3)	17.8 (7.6, 47.8)	0.009
Women (N)	74	35	67	132	
Total cholesterol	197 (174, 223)	201 (171, 235)	201 (168, 232)	202 (181, 231)	0.55
LDL cholesterol	124 (101, 145)	125 (104, 146)	122 (99, 149)	126 (104, 153)	0.65
HDL cholesterol	45 (37, 55)	44 (36, 57)	47 (41, 58)	52 (44, 63)	0.002
Triglycerides	125 (93, 161)	146 (93, 172)	136 (99, 193)	105 (83, 151)	0.003
Lipoprotein(a)	22.0 (8.8, 66.1)	16.1 (9.1, 56.0)	17.0 (7.5, 47.8)	14.1 (7.0, 41.6)	0.13

^a Plasma lipid values in mg/dL^b Data presented in medians and interquartile ranges^c P calculated with Wilcoxon Rank-Order Sum test

Table 3

Association of Plasma Lipids to Adenoma Risk

	Controls	Single small adenomas	OR ^b	95% CI	Multiple small adenomas	OR ^b	95% CI	Advanced adenomas	OR ^b	95% CI
Total cholesterol										
Q1 143 (89–160) ^a	98	58	1.00	reference	56	1.00	reference	59	1.00	reference
Q2 177 (161–191)	103	78	1.37	0.83, 2.24	52	1.37	0.68, 2.78	80	1.30	0.71, 2.40
Q3 202 (192–216)	99	52	0.98	0.57, 1.69	30	1.00	0.47, 2.13	60	1.26	0.69, 2.33
Q4 238 (217–295)	103	58	0.91	0.52, 1.58	41	1.47	0.68, 3.17	55	0.83	0.43, 1.59
<i>P</i> trend				0.64			0.46			0.50
LDL cholesterol										
Q1 80 (37–93)	98	58	1.00	reference	62	1.00	reference	65	1.00	reference
Q2 105 (94–115)	103	67	1.47	0.82, 2.65	34	0.68	0.35, 1.34	63	0.86	0.47, 1.57
Q3 129 (116–145)	101	77	1.48	0.87, 2.52	44	1.23	0.60, 2.52	81	1.05	0.59, 1.88
Q4 157 (146–215)	101	44	0.84	0.46, 1.53	39	1.04	0.52, 2.05	45	0.70	0.37, 1.34
<i>P</i> trend				0.66			0.71			0.42
HDL cholesterol										
Q1 29 (12–34)	98	72	1.00	reference	79	1.00	reference	98	1.00	reference
Q2 38 (35–41)	94	61	0.88	0.48, 1.59	50	0.75	0.37, 1.45	94	0.63	0.33, 1.18
Q3 46 (42–51)	106	69	0.79	0.41, 1.52	30	0.42	0.18, 0.96	106	0.37	0.19, 0.74
Q4 60 (52–106)	105	44	0.49	0.23, 1.07	20	0.35	0.13, 0.91	105	0.22	0.09, 0.54
<i>P</i> trend				0.06			0.02			0.0005
Triglycerides										
Q1 71 (40–84)	96	30	1.00	reference	18	1.00	reference	26	1.00	Reference
Q2 102 (85–119)	104	56	1.31	0.70, 2.46	38	1.41	0.57, 3.49	66	3.25	1.48, 7.17
Q3 141 (120–177)	101	72	1.84	0.96, 3.53	69	1.56	0.66, 3.70	81	3.33	1.46, 7.60
Q4 232 (178–721)	102	88	2.40	1.26, 4.55	54	1.67	0.66, 4.23	81	2.79	1.25, 6.23
<i>P</i> trend				0.005			0.40			0.32
Lipoprotein (a)										
Q1 4.1 (0.3–7.3)	100	73	1.00	reference	53	1.00	reference	74	1.00	Reference
Q2 11.0 (7.4–16.9)	101	63	1.26	0.74, 2.15	52	1.20	0.59, 2.40	61	0.83	0.46, 1.50
Q3 25.5 (17.1–44.8)	101	62	0.91	0.54, 1.53	33	0.47	0.22, 1.03	59	1.02	0.57, 1.82

Controls	Single small adenomas	OR ^b	95% CI	Multiple small adenomas	OR ^b	95% CI	Advanced adenomas	OR ^b	95% CI
Q4 69.8 (45.6–115.6)	48	0.73	0.40, 1.36	41	0.71	0.34, 1.48	60	0.80	0.44, 1.47
<i>P</i> trend			0.15			0.26			0.58

^a Plasma lipid values in mg/dL, median (range)

^b Models adjusted for age, body mass index, alcohol use, tobacco use, physical activity, use of HRT, indication for colonoscopy, regular NSAID use, and study site

Table 4
Association of Plasma Lipids to Adenoma Risk-Participants with Complete Information regarding Statin Medication Use^a

	Controls	Single Small Adenoma	OR ^c	95% CI	Multiple Small Adenomas	OR ^c	95% CI	Advanced adenomas	OR	95% CI
Total cholesterol										
Q1 143 (89,160) ^b	79	53	1.00	reference	46	1.00	reference	46	1.00	reference
Q2 177 (161, 191)	81	78	1.58	0.94, 2.66	40	1.37	0.62, 3.02	64	1.46	0.71, 3.03
Q3 201 (192, 216)	77	50	1.06	0.58, 1.92	25	1.31	0.54, 3.19	49	1.68	0.76, 3.72
Q4 238 (217, 295)	83	53	0.84	0.45, 1.57	33	1.62	0.63, 4.13	45	0.94	0.41, 2.15
<i>P</i> trend				0.52			0.33			0.83
LDL										
Q1 79 (37, 93)	80	53	1.00	reference	50	1.00	reference	51	1.00	reference
Q2 105 (94, 114)	78	64	1.94	1.01, 3.73	27	0.80	0.38, 1.70	50	1.10	0.53, 2.27
Q3 128 (115, 145)	82	78	1.82	1.01, 3.27	34	1.53	0.64, 3.60	69	1.60	0.75, 3.41
Q4 157 (146, 215)	80	39	0.80	0.40, 1.56	33	1.28	0.54, 3.06	34	0.78	0.33, 1.83
<i>P</i> trend				0.61			0.46			0.85
HDL										
Q1 28 (12, 33)	73	56	1.00	reference	60	1.00	reference	68	1.00	reference
Q2 37 (34, 41)	77	72	1.17	0.63, 2.17	42	0.71	0.32, 1.56	70	0.92	0.44, 1.95
Q3 46 (42, 52)	87	66	0.96	0.47, 1.98	30	0.68	0.26, 1.83	42	0.53	0.23, 1.20
Q4 62 (53, 106)	83	40	0.61	0.26, 1.41	12	0.29	0.08, 1.01	24	0.15	0.05, 0.45
<i>P</i> trend				0.08			0.06			0.0007
Triglycerides										
Q1 73 (40, 85)	78	29	1.00	reference	14	1.00	reference	21	1.00	Reference
Q2 102 (86, 119)	81	53	1.48	0.78, 2.78	31	1.40	0.49, 4.01	54	3.70	1.44, 9.52
Q3 142 (120, 177)	81	70	2.21	1.15, 4.25	55	1.27	0.47, 3.44	63	3.99	1.49, 10.66
Q4 243 (178, 721)	80	82	2.43	1.28, 4.61	44	1.59	0.55, 4.63	66	2.70	1.01, 7.24
<i>P</i> trend				0.01			0.48			0.69
Lipoprotein (a)										
Q1 3.7 (0.3, 7.1)	79	68	1.00	reference	43	1.00	reference	59	1.00	Reference
Q2 10.6 (7.3, 16.9)	81	63	1.12	0.64, 1.96	41	1.35	0.62, 2.94	52	0.95	0.49, 1.85
Q3 25.2 (17.1, 40.9)	80	54	0.78	0.44, 1.39	29	0.61	0.25, 1.45	42	1.03	0.50, 2.08

	Controls	Single Small Adenoma	OR ^c	95% CI	Multiple Small Adenomas	OR ^c	95% CI	Advanced adenomas	OR	95% CI
Q4 66.1 (41.5, 115.6)	80	49	0.81	0.42, 1.55	31	0.82	0.36, 1.87	51	1.23	0.59, 2.54
<i>P</i> trend				0.25			0.51			0.74

^aN = 902

^bPlasma lipid values in mg/dL

^cModels adjusted for age, body mass index, alcohol use, tobacco use, physical activity, use of HRT, indication for colonoscopy, regular NSAID use, study site, and use of statin medication