Serum Lipids and Adenomas of the Left Colon and Rectum¹

Crissy L. Bird,² Sue A. Ingles, Harold D. Frankl, Eric R. Lee, Matthew P. Longnecker, and Robert W. Haile

Department of Preventive Medicine, School of Medicine, University of Southern California, Los Angeles, California 90033 [C. L. B., S. A. I., R. W. H.]; Divisions of Gastroenterology at the Sunset [H. D. F.] and Bellflower [E. R. L.] Kaiser Permanente Medical Centers, Los Angeles, California 90027; and National Institute of Environmental Health Sciences Epidemiology Branch, Research Triangle Park, North Carolina 27709 [M. P. L.]

Abstract
Levels of serum lipids are partially determined by several established risk factors for colorectal cancer and are themselves potential risk factors for the disease. However, evaluating serum lipids as risk factors has proved problematic because metabolic events associated with malignant transformation or progression appear to alter serum lipid concentrations. Serum lipid concentrations are less likely to have altered in individuals with precancerous lesions, such as colorectal adenomas. During 1991–1993, we collected fasting blood samples from and provided questionnaires to men and women 50–75 years old, who visited sigmoidoscopy clinics at a health maintenance organization. Serum lipid concentrations from 486 cases with adenomas and 520 controls were analyzed. Compared to subjects in the lowest quintile of serum triglyceride concentrations, subjects in the highest quintile had an adjusted odds ratio of 1.5 (95% confidence interval, 1.0–2.2). The corresponding odds ratio for total cholesterol was 1.3 (0.9–1.9); for high-density lipoprotein cholesterol, it was 1.1 (0.7–1.6); and for low-density lipoprotein cholesterol, it was 1.1 (0.7–1.6). Further adjustment for potential confounding did not alter these results substantially, although determinants of serum triglycerides and high-density lipoprotein cholesterol (e.g., obesity, physical activity, and refined carbohydrate and alcohol intake) in this and other studies may not be sufficiently well measured to avoid residual confounding. Higher levels of serum triglycerides are associated with an increased risk of adenomatous polyps. Consistent with previous studies, serum cholesterol was not inversely related to the risk of colorectal polyps.

Introduction
High serum levels of total cholesterol, LDL-C³ or triglycerides, or low serum levels of HDL-C are very common in individuals pursuing Western lifestyles. The combined undesirable lipid profile is especially common in obesity (1), whereas lack of exercise and several attributes of Western diets (e.g., high intakes of saturated fat, refined carbohydrates, and alcohol) appear to alter levels of individual lipids (2). Many of these determinants of serum lipid levels are established risk factors for colorectal cancer (3, 4).

Contrary to expectations, the association of low serum cholesterol with colorectal cancer and other cancers has frequently been observed and is a source of ongoing controversy (5). It has been suggested that some cholesterol-lowering diets may increase the risk of colorectal cancer (6), but the association may be explained by reductions in serum cholesterol due to undetected malignancy, inflammation, or other factors unrelated to diet (5, 7–10). Adenomatous polyps are lesions widely believed to be early neoplastic precursors to colorectal cancer (11), unlikely to have affected levels of blood analytes. Examining these polyps and their relationship to cholesterol and other serum lipids may thus help resolve the colorectal cancer-cholesterol controversy. To date, serum cholesterol levels have not been positively associated with adenoma risk. If anything, serum cholesterol has tended to be higher (12–16) and atherosclerotic lesions more extensive (17, 18) in adenoma cases than controls, although this has not always held up on further evaluation (15, 19). Unfortunately, these studies have been small or have lacked data on other serum lipids and potentially important covariates. The potential importance of other serum lipids was suggested in a small clinical trial a few years ago (4). Concentrations of serum triglycerides and fecal bile acids were found to be associated with each other, both exposures exhibiting J-shaped associations with polyp recurrence (4). With this in mind, we examined serum lipids in relation to adenomatous polyps in a case-control study of outpatients undergoing sigmoidoscopy, taking into account possible effects of such factors as diet, obesity, physical activity, and several biochemical markers of nutritional status.

Materials and Methods
Subjects were eligible for the study if they underwent screening using flexible sigmoidoscopy at either of two Southern California Kaiser Permanente medical centers from January 1, 1991 through August 25, 1993. Eligible men and women were 50–75 years old, were free of invasive cancer, inflammatory bowel disease, and familial polyposis; were fluent in English; had no previous bowel surgery or history of polyps; were residents of Los Angeles or Orange County; and had no physical or mental disability precluding an interview. In addition, subjects who

¹The abbreviations used are: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

© 1996 American Association for Cancer Research. cebp.aacrjournals.org Downloaded from on November 6, 2017.
Serum Lipids and Colorectal Adenomas

had symptoms suggestive of organic intestinal disease were excluded. Cases were subjects diagnosed for the first time with one or more histologically confirmed adenomatous polyps. Controls had no adenomas or polyps of any other type discovered at sigmoidoscopy and were individually matched to cases by gender, age (within 5-year categories), date of sigmoidoscopy (within 3-month periods), and Kaiser center. The average depth of the sigmoidoscopic examination was 55 ± 11 cm (SD) for cases and 59 ± 5 cm for controls. This was a case-control study of polyps with regard to the rectosigmoid region only, since controls did not undergo colonoscopy. However, most carcinomas arising from polyps may arise from polyps in the rectosigmoid region (20).

Further details of subject recruitment and data collection have been provided elsewhere (21, 22). Briefly, polyp data were obtained from Kaiser pathology reports. Dietary intakes from food and supplements were assessed by means of a mailed, semiquantitative food frequency questionnaire (22–24). Data on a variety of nondietary risk factors were obtained during a script-standardized in-person interview given on average 5 months after sigmoidoscopy.

Serum Lipids and Other Blood Indicators. A fasting blood sample was drawn in the morning, on average 6 months after sigmoidoscopy, into a plain Vacutainer tube. Phlebotomy was refused by 29 of 529 recruited cases and 30 of 563 recruited controls (628 cases and 689 controls were initially identified as eligible to be in the study), yielding a response rate (number drawn/number eligible) of 80% for cases and 77% for controls (21). The sample was shipped on ice to a single regional Kaiser Permanente laboratory and then centrifuged, and the serum was assayed the same day. Usually only one sample was assayed in each batch of assays (along with samples unrelated to the study). All assays were conducted by medical technologists who were blinded as to case-control status. Serum cholesterol, HDL-C, and triglyceride samples were assayed using enzymatic methods (Boehringer Mannheim Diagnostics, Indianapolis, IN) on a Hitachi 747 autoanalyzer (Hitachi Denshi American Ltd., Compton, CA). LDL-C values were calculated from serum total cholesterol, HDL-C, and triglyceride concentrations using the Friedewald formula (25).

Commercially assayed and unassayed control samples (Lyphochek, levels 1 and 2; Bio-Rad Laboratories, Hercules, CA) were included in each batch of serum lipid assays to monitor accuracy and precision. Results obtained using assayed control samples (normal and abnormal; Boehringer Mannheim) were routinely checked during each work shift.

Other nutritional indicators measured were: plasma carotenoids, whole-blood ascorbate, plasma folate, RBC folate, and plasma ferritin. Samples for these assays were centrifuged and treated with stabilizing agents, if needed, and stored at -70°C. Plasma carotenoid samples were assayed via high-performance liquid chromatography. Whole-blood ascorbate samples were assayed using a spectrophotometric bis-2,4-diphenylhydrizine method. Folate and ferritin assays have been described elsewhere (22, 26).

Statistical Analysis. Serum lipid values were obtained for 1022 subjects, of whom 2 were dropped from the data set because a serum cholesterol, HDL, or triglyceride result was missing. Another 14 subjects were excluded because they lacked dietary questionnaires. The final data set contained 431 matched pairs as well as unmatched controls (n = 89) and cases (n = 55). The latter generally occurred when one subject in a pair did not provide a blood sample, but a few occurred for other reasons (e.g., nonfluent in English).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Means (SDs) or percentages of relevant variables describing the sigmoidoscopy study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Cases (n = 486)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.1 (6.8)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>65.2</td>
</tr>
<tr>
<td>Exercisers (%a)</td>
<td>23.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 (4.5)</td>
</tr>
<tr>
<td>Caloric intake (kcal/day)b</td>
<td>2033 (853)</td>
</tr>
<tr>
<td>Dietary fiber (g/day)c</td>
<td>19.2 (9.7)</td>
</tr>
<tr>
<td>Saturated fat (g/day)d</td>
<td>25.2 (13.2)</td>
</tr>
<tr>
<td>Smokers (%e)</td>
<td>30.2</td>
</tr>
<tr>
<td>Alcohol (% drinking ≥7 g ethanol/day)f</td>
<td>30.9</td>
</tr>
</tbody>
</table>

* For variables expressed as means, the P value was obtained using Student’s t test comparing cases and controls. For variables expressed as percentages, it was obtained using the x² test.

Serum lipid values were divided into quintiles, using their distributions across all subjects. A conditional logistic regression model (n = 431 pairs) was fit to a serum lipid term, with and without potential confounding variables. The matching was then broken, and unconditional logistic regression models were fit, stratifying on the matching variables, the same potential confounders, and using the same 862 subjects. The conditional and unconditional analyses yielded similar results, which was expected since they both controlled for the matching variables (27). Next, unconditional models with all 1006 subjects (including the unmatched) were examined. These models also gave similar results. Results reported in this article are from unconditional models that included all subjects on whom we had information.

Results

This was an ethnically diverse study population consisting of 169 female cases, 173 female controls, 317 male cases, and 347 male controls, of whom 54% were white, 19% were Latino, 16% were black, and 11% were Asian/Pacific Islanders. Ethnicity, education, and income did not vary appreciably between cases and controls (data not shown). Results obtained from cases and controls for major covariates of interest are presented in Table 1.

Table 2 shows medians and ranges of the serum lipids. The median serum triglyceride concentration was higher in cases than in controls, significantly so among female subjects. There were no marked differences between cases and controls with regard to the other serum lipids.

Table 3 shows the odds ratios for the association of quintiles of serum lipids with colorectal polyps. Polyp risk was increased in subjects in the highest quintile of serum triglycerides relative to those in the lowest quintile. In models that adjusted for the matching variables only, no serum lipid other than the serum triglycerides appeared to be related to polyp prevalence, although there was a suggestion of increased risk of polyps in the highest quintile of serum cholesterol levels. Fur-
Further adjusted for serum triglycerides was restricted to men.

Serum lipids associations with polyps were examined according to the location (left colon versus rectum) and size (<1 cm versus >1 cm in diameter) of each case's largest adenoma. No clear difference in results due to polyp location was found (data not shown). Although confidence intervals were wide, both the serum triglyceride and serum cholesterol associations with large polyps were stronger than with small polyps. For large polyps (89 cases), odds ratios (95% confidence intervals) across quintiles for serum triglycerides adjusted for the matching variables were 1.0 (lowest), 2.7 (1.2–5.8), 2.0 (0.9–4.6), 1.6 (0.7–3.7), and 2.1 (0.9–4.8); for small polyps (391 cases), they were 1.0, 0.9 (0.6–1.3), 0.9 (0.6–1.4), 1.1 (0.7–1.6), and 1.4 (1.0–2.2). For large polyps, odds ratios across quintiles for serum cholesterol adjusted for the matching variables were 1.0 (lowest), 0.8 (0.4–1.9), 1.6 (0.8–3.3), 1.2 (0.6–2.6), and 1.8 (0.9–3.7); for small polyps, they were 1.0, 0.9 (0.6–1.4), 1.0 (0.7–1.6), 1.0 (0.7–1.6), and 1.2 (0.8–1.9).

The associations of the serum lipids with some of the lifestyle variables known to influence their concentrations were examined. In this study population, serum triglycerides were associated with the body mass index (Pearson's r = 0.20, P = 0.0001). Serum HDL-C was associated with the body mass index (r = −0.20, P = 0.0001) and ethanol intake (r = 0.10, P = 0.0004). Both serum lipids were also associated with exercise: using Student's t test, serum triglycerides averaged 15.6 mg/dl lower in subjects who exercised vigorously at least three times per week than in sedentary subjects (P = 0.03), and serum HDL-C averaged 2.3 mg/dl higher in exercisers (P = 0.04). Neither variable appeared to be associated with intakes of calories, dietary fiber, carbohydrate, sucrose, saturated fat, or the red meat:chicken/fish ratio. There was a trend toward an association with cigarette smoking: using Student's t test, serum triglycerides averaged 17.3 mg/dl higher in smokers than in nonsmokers (P = 0.07), while serum HDL-C averaged 1.6 mg/dl lower in smokers (P = 0.15). Not surprisingly, serum triglycerides and serum HDL-C were associated with each other (Pearson’s r = −0.40, P = 0.0001).
Serum Lipids and Colorectal Adenomas

Finally, no substantial difference in results was observed when different serum lipid categories were modeled, such as quintiles defined within gender. Serum lipid results were not appreciably altered when we adjusted for family history of colorectal cancer, race, plasma β-carotene, RBC folate, whole-blood ascorbate, known previous negative sigmoidoscopy examination, or for time elapsed between sigmoidoscopy and blood sample collection. Odds ratios were not altered when terms for the red meat to chicken:fish ratio or for the number of days between sigmoidoscopy and blood sample collection. Results were also similar when we stratified on whether subjects said they had (n = 206) or had not made a major dietary change between sigmoidoscopy and blood sample collection.

Discussion
Of the serum lipids examined, only the triglyceride fraction was associated with the prevalence of adenomas in a simple adjusted model as well as in a more complex model containing several potential confounding variables (Table 3). Total serum cholesterol was not inversely associated with risk, as has been reported in some studies of colorectal cancer. The results for calculated LDL-C levels were similar to those for total serum cholesterol. HDL-C was not associated with polyp prevalence, except for a positive association that appeared among men after adjustment for serum triglycerides. Adjustment for a variety of potential confounders, including several biochemical measures of nutritional status, did not change serum lipid results. However, terms for physical activity and obesity (body mass index) were influential in serum triglyceride models. Also, serum HDL-C and serum triglycerides were mutually influential when in the same model.

Physical activity and obesity are determinants of serum triglyceride levels (30). These risk factors may also influence colorectal neoplasia independently of serum triglycerides, e.g., by influencing serum insulin levels (28). To adjust for potential confounding, we included the body mass index and a term for physical activity in serum triglyceride models. However, existing methods may only crudely measure etiologically relevant aspects of obesity and physical activity (28, 31, 32). Because of potential residual confounding, it is still possible that obesity or physical activity was partially or entirely responsible for the association of serum triglycerides with adenoma risk.

Including terms for serum triglycerides and HDL-C in the same model strengthened the triglyceride-polyp association in all subjects and produced a positive association of HDL-C with polyps in men. In population studies, serum triglycerides and serum HDL-C are inversely associated, and it is thought that serum triglycerides partially determine HDL-C levels (30). In addition, several factors concurrently decrease HDL-C and increase triglyceride levels, including inactivity, obesity, and high intakes of calories/fat and refined carbohydrates (4, 30). Therefore, mutual adjustment of serum triglycerides and HDL-C may have eliminated some residual confounding due to these factors. One result may have been the elimination of negative confounding of HDL-C odds ratios by physical activity. In contrast, alcohol consumption can increase both serum HDL-C and triglycerides, but serum HDL-C is much more sensitive to alcohol intake than are serum triglycerides (33). Consequently, adjustment of HDL-C for triglyceride level would not have eliminated confounding due to alcohol. Alcohol intake was weakly associated with adenoma prevalence in this study (34). Although we adjusted all serum lipids for ethanol intake, residual confounding of HDL-C by ethanol intake may explain the positive association of HDL-C and polyps in men. The association was not observed in women, possibly because women do not drink as regularly or as heavily as men (35).

The few previous reports evaluating the associations of serum lipids and colorectal adenomas have mainly been case-control studies with widely differing study populations and with fewer than 250 cases. However, their results were reasonably similar to ours. No study found an inverse association of serum cholesterol with polyps risk (12–16, 19). Of these studies, four found some evidence of a positive association (12–15), although this did not always persist on further evaluation (15, 19), and one study found no association (16). Only two studies

### Table 4 Gender-specific odds ratios for the association of quintiles of serum triglycerides and HDL-C with colorectal polyps

| Serum triglycerides | Women | Men | Odds ratios (95% confidence intervals) | P trend
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted</td>
<td>Further adjusted</td>
<td>Adjusted</td>
<td>Further adjusted</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;95</td>
<td>95–121</td>
<td>122–157</td>
<td>158–210</td>
</tr>
<tr>
<td>Adjusted*</td>
<td><strong>1.0</strong></td>
<td><strong>1.0 (0.5-1.8)</strong></td>
<td><strong>0.9 (0.4-1.8)</strong></td>
<td><strong>1.2 (0.6-2.4)</strong></td>
</tr>
<tr>
<td>Further adjusted</td>
<td><strong>1.0</strong></td>
<td><strong>0.8 (0.4-1.6)</strong></td>
<td><strong>0.8 (0.4-1.8)</strong></td>
<td><strong>1.2 (0.5-2.5)</strong></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;37</td>
<td>37–42</td>
<td>43–50</td>
<td>51–60</td>
</tr>
<tr>
<td>Adjusted*</td>
<td><strong>1.0</strong></td>
<td><strong>0.6 (0.2-1.7)</strong></td>
<td><strong>0.4 (0.2-1.1)</strong></td>
<td><strong>0.5 (0.2-1.1)</strong></td>
</tr>
<tr>
<td>Further adjusted</td>
<td><strong>1.0</strong></td>
<td><strong>0.7 (0.2-2.3)</strong></td>
<td><strong>0.6 (0.2-1.7)</strong></td>
<td><strong>0.9 (0.3-2.7)</strong></td>
</tr>
</tbody>
</table>

*Unconditional logistic regression models fitted to quintiles of serum lipids and reported by gender (females, 169 cases and 173 controls; males, 317 cases and 347 controls).

_**_P_ value for trend across quintiles based on serum lipid coefficients in models above._

*Further adjusted using the potential confounding variables: smoking, body mass index, exercise, calories, dietary fiber, saturated fat, alcohol intake, and quintile level of HDL-C.*

*Further adjusted using the potential confounding variables: smoking, body mass index, exercise, calories, dietary fiber, saturated fat, alcohol intake, and quintile level of HDL-C.*

---

One mg/dl serum total or HDL-C = 0.02586 mm. One mg/dl serum triglycerides = 0.01129 mm. All models in this table are adjusted for the matching variables (age, sex, Kaiser location, and date of sigmoidoscopy).
examined serum LDL-C: one study reported a positive association with polyps (12) and the other no association (19). Serum HDL-C was examined and found to be inversely associated with polyps risk in two studies (12, 13), but the association did not persist when Kono et al. (13) had accumulated a larger study population (19). Serum triglycerides were also initially associated with polyps in the study by Kono et al. (13), but, in contrast to the present study, these authors found that the association was eliminated when an HDL-C term was included in the model. Because within-person variation in serum triglyceride concentrations is much greater than for other serum lipids, nondifferential misclassification of triglyceride levels is potentially much greater. Therefore, attenuation of a serum triglyceride-disease association after adjustment for other serum lipids does not rule out a possible triglyceride effect (30).

In the one other study with data relevant to serum triglycerides, investigators observed a positive relationship between polyps and the highest quintile of very low-density cholesterol (13), a lipid fraction closely associated with triglycerides in serum (36).

In addition to the case-control studies, one clinical trial has reported an association between serum triglyceride levels and the risk of adenomatous polyps in a small sample of subjects. Baseline serum triglyceride concentrations were higher in 45 subjects with a history of having adenomas than in those with no such history (4). Serum triglycerides were later found to be associated with poly recurrence among 126 subjects in the clinical trial (4).

A high serum triglyceride level may reflect other aspects of metabolism that are procarcinogenic (4). For example, after ileal resection or treatment with cholestyramine, serum triglyceride concentrations increase when bile acid synthesis increases (37, 38). The reason for this is unknown, but it is thought that the serum triglyceride increase is a side effect of increased activity in the bile acid synthetic pathway (38). Experimental evidence and some epidemiological evidence suggests that metabolites of colonic bile acids may be carcinogenic (39, 40). Perhaps, high serum triglyceride concentrations in healthy individuals are often indicative of a high rate of bile acid synthesis. An increase in bile acids synthesized and secreted may provide abundant substrate for formation of secondary bile acids and thereby promote carcinogenesis in the large bowel.

The present study had several potential weaknesses. Only adenomas of the left colon and rectum were examined. However, results should be relevant to etiological relationships that are not unique to the proximal colon. In common with most epidemiological studies, serum lipids were measured on only one occasion. Large within-individual variation is a problem in measurement of serum triglycerides (30). Thus, although we observed an association of serum triglycerides with polyps, the magnitude of that association may be greater than reported here. Also, currently available methods for measuring covariates such as physical activity, obesity, and intakes of alcohol, fat, calories, and carbohydrates are both crude and imprecise, and we did not have a measure of central obesity. Consequently, we cannot rule out the possibility that physical activity, obesity, and diet are responsible for the triglyceride “effect” or that the serum HDL-C odds ratios may be biased by misclassified alcohol intakes. Finally, measurement of serum lipids occurred an average of 6 months after sigmoidoscopy. It is possible that serum lipid levels changed subsequent to cases undertaking lifestyle reforms. However, results were unaltered when we adjusted for time elapsed from sigmoidoscopy to phlebotomy, or for reported dietary change, and we have not found evidence of a postdiagnostic change in the blood levels of nutrients (22, 26).

Nonetheless, this study had several important advantages over past studies of serum lipids and colorectal neoplasia. There was a large number of male and female subjects, cases and controls were all insures of a single health maintenance organization, and the recruitment rate was high (21). Protopathic bias was minimized because subjects tended to be asymptomatic outpatients referred for routine screening (21) and because cases had adenomas, not cancer. Also, questionnaire and biochemical data were available on an unusually large number of variables, allowing an extensive evaluation of confounding.

Serum triglycerides and serum HDL-C were both associated with adenomas in at least some models in this study, but, in our opinion, only the serum triglyceride association is convincing. Serum triglycerides were associated with colorectal adenomas in the simplest model as well as in the most complete model. The triglyceride-polyp association was present in both men and women (Tables 2 and 4), albeit weakly in men. Furthermore, previous studies provide some evidence of a positive relationship between serum triglycerides and adenomas. By contrast, the association of serum HDL-C with adenomas appeared only when a term for serum triglycerides was added to the model, the association was present only in men, and it may potentially be explained by residual confounding due to alcohol intake. Previous studies have not provided any support for a positive association of HDL-C with polyps.

We conclude that the serum triglyceride concentration is potentially a useful risk factor for colorectal neoplasia. This may be true even if physical activity, diet, and obesity are shown to be the mediators of this risk.

References


Downloaded from cebp.aacrjournals.org on November 6, 2017. © 1996 American Association for Cancer Research.
Serum lipids and adenomas of the left colon and rectum.

C L Bird, S A Ingles, H D Frankl, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/5/8/607

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.