Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition

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Revised 20 December 2010
Accepted 14 January 2011
Published Online First
7 March 2011

ABSTRACT

Objective To examine the association between serum concentrations of total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol, triglycerides, apolipoprotein A-I (apoA), apolipoprotein B and the incidence of colorectal cancer (CRC).

Design Nested case–control study.

Setting The study was conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort of more than 520 000 participants from 10 western European countries.

Participants 1238 cases of incident CRC, which developed after enrolment into the cohort, were matched with 1238 controls for age, sex, centre, follow-up time, time of blood collection and fasting status.

Main outcome measures Serum concentrations were quantitatively determined by colorimetric and turbidimetric methods. Dietary and lifestyle data were obtained from questionnaires. Conditional logistic regression models were used to estimate incidence rate ratios (RRs) and 95% CIs which were adjusted for height, weight, smoking habits, physical activity, education, consumption of fruit, vegetables, meat, fish, alcohol, fibre and energy.

Results After adjustments, the concentrations of HDL and apoA were inversely associated with the risk of colon cancer (RR for 1 SD increase of 16.6 mg/dl in HDL and 32.0 mg/dl in apoA of 0.78 (95% CI 0.68 to 0.89) and 0.82 (95% CI 0.72 to 0.94), respectively). No association was observed with the risk of rectal cancer. Additional adjustment for biomarkers of systemic inflammation, insulin resistance and oxidative stress or exclusion of the first 2 years of follow-up did not influence the association between HDL and risk of colon cancer.

Conclusions These findings show that high concentrations of serum HDL are associated with a decreased risk of colon cancer. The mechanism behind this association needs further elucidation.

Significance of this study

What is already known about this subject?

- Epidemiological studies have suggested that the metabolic syndrome is associated with risk of colorectal cancer (CRC), but only a few studies have explored the dyslipidaemia component of the metabolic syndrome in relation to the risk of CRC.
- Findings of total cholesterol and triglycerides on the risk of CRC have been inconsistent.
- Data on high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol, apolipoprotein A-1 (apoA) and apolipoprotein B in relation to risk of CRC are limited.

What are the new findings?

- In a western European population, for the first time, higher pre-diagnostic HDL and apoA concentrations were statistically significantly inversely associated with risk of colon cancer, but not rectal cancer.
- Only the association between HDL concentrations and risk of colon cancer remained after exclusion of the first 2 years of follow-up.
- As adjustments for biomarkers of systemic inflammation, insulin resistance and oxidative stress did not influence the association between HDL and risk of colon cancer, further investigations are needed to clarify the exact role of HDL in colon carcinogenesis.

How might it impact on clinical practice in the foreseeable future?

- If confirmed, levels of HDL may be used, in addition to other modifiable risk factors already applied in clinical practice, to advise patients about changing their lifestyle.

INTRODUCTION

Dyslipidaemia is a pathological alteration of lipid and lipoprotein concentrations in the blood and is part of the metabolic syndrome.[1] Epidemiological studies have shown that persons with the metabolic syndrome have an increased risk of colorectal cancer (CRC).[1] Few studies, however, have explored the dyslipidaemia component of the metabolic syndrome—that is, lipid and lipoprotein concentrations by themselves—in relation to CRC risk.

The main focus of these studies was the association of blood concentrations of total cholesterol (TC) and triglycerides (TG) in relation to CRC risk. A case–control study in Korea by Chung *et al* showed an inverse association between these lipids and the risk of CRC.[2] Findings from three prospective studies on TC concentrations have been inconsistent, showing either a positive association with CRC, colon and rectal cancer risk,[3] no association with the risk of colon cancer but a positive association with the risk of rectal cancer in men only,[4] or no association at all.[5] As far as TG concentrations are concerned, three cohort studies found no significant associations with risk of CRC,[6–8] colon[8 9] or rectal[8 9] cancer. Data on high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) or their respective components apolipoprotein A-1 (apoA) and apolipoprotein B (apoB) are scarce.

There are several possible mechanisms whereby serum lipids and lipoproteins may influence CRC. Lipids and lipoproteins have been associated with neoplastic processes such as inflammation,[10] insulin resistance[11] and oxidative stress.[12 13] However, whether lipids and lipoproteins cause these processes or are intermediate or correlated factors within these pathways is unknown. Similarly, dietary and lifestyle factors such as smoking,[14] obesity,[15] physical inactivity,[16] a high fat/low fibre diet[17] and higher alcohol consumption[18] also influence lipid and lipoprotein concentrations unfavourably. Therefore, altered lipid and lipoprotein concentrations may be a consequence or corollary of an unhealthy lifestyle rather than a direct initial component cause in the chain of events leading to CRC.

A nested case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) study was conducted to investigate the associations between serum concentrations of lipids and lipoproteins and the risk of CRC. In addition, further analyses were performed to evaluate whether the observed associations were independent of the metabolic syndrome and/or of blood concentrations of biomarkers for systemic inflammation (C reactive protein (CRP)), insulin resistance (C peptide, glycosylated haemoglobin (HbA1c)) and oxidative stress (reactive oxygen metabolites (ROM)).

METHODS

Study population

The rationale and methods of the EPIC study have been reported in detail previously.[19 20] In brief, EPIC is a multicentre prospective cohort study designed to investigate the relation between diet, various lifestyle and environmental factors and the incidence of different forms of cancer. It consists of cohorts in 23 centres from 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. A total of 521 448 subjects, about 70% women and mostly aged 35–70 years, joined the study between 1992 and 2000. Participants completed dietary[20] and lifestyle questionnaires, had their anthropometric measurements recorded (self-reported in France, Norway and Oxford) and donated a blood sample. These blood samples were processed, aliquoted and stored in heat-sealed straws at −196°C under liquid nitrogen at the International Agency for Research on Cancer (IARC) for all countries except Denmark (where tubes were stored at −150°C under nitrogen vapour) and Sweden (where they were stored in freezers at −80°C).

End points

This analysis included data on cancer cases assembled at the central database at IARC before April 2004. Incident cancer cases were identified through record linkage with regional cancer registries in Denmark, Norway, the Netherlands, Spain, Sweden, the UK and in most of the Italian centres. In France, Germany, Greece and Naples (Italy), follow-up was based on a combination of methods including health insurance records, cancer and pathology registries and active follow-up through study subjects and their next of kin. Closure dates for the present study were defined as the latest date of complete follow-up for both cancer incidence and vital status, and ranged from December 1999 to June 2003 for centres using registry data and from June 2000 to December 2002 for centres using active follow-up procedures.

Nested case–control design

Right or proximal colon tumours included the caecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure (C18.0–18.5 of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems). Left colon tumours included the descending (C18.6) and sigmoid colon (C18.7). Overlapping lesions of the colon (C18.8) and colon not otherwise specified (NOS; C18.9) were grouped among all colon cancers only (C18.0–C18.9). Cancer of the rectum included tumours occurring at the rectosigmoid junction (C19) and rectum (C20).

After exclusions (20 cases who had in situ tumours or tumours of non-malignant morphology, 2 cases who had a secondary tumour), a total of 1238 first incident CRC cases (779 colon cancer, 459 rectal cancer) with available questionnaire data and blood samples were identified for the present study. The distribution of cases (colon/rectum) by country was Denmark 184/166; France 24/8; Greece 12/13; Germany 93/55; Italy 104/41; The Netherlands 91/47; Spain 79/42; Sweden 41/25; UK 151/62. Cases were not selected from Norway because blood samples were only recently collected and few cases were diagnosed after blood donation, and the Malmö centre of Sweden because the amount of blood sample per subject was limited.

Control subjects were selected by incidence density sampling from all cohort members alive and free of cancer at the time of diagnosis of the matching case and were matched to cases by study centre, sex, follow-up time, age at blood collection (±2 years), time of blood collection (±4 h) and fasting status at the time of blood collection (<3 h (not fasting), 3–6 h (in between) or >6 h (fasting)). Women were further matched by menopausal status (premenopausal, perimenopausal/unknown or postmenopausal),[21] menstrual cycle (follicular early/late, ovulatory or luteal early/late)[22] and current pill or postmenopausal hormone therapy use (no, yes or unknown). The latter matching criteria in women were of necessity to other EPIC nested case–control studies that were being conducted using the same matched case–control sets. For every case one matched control was identified.

Laboratory measurements

The reliability of measuring lipids and lipoproteins in EPIC samples has previously been determined[23] and the Spearman

rank correlation coefficients between two time points ranged between 0.62 and 0.78. Serum TC and TG were quantitatively determined by a colorimetric method and HDL and LDL were determined in a homogenous assay with a colorimetric end point. ApoA and ApoB were determined by turbidimetric methods. All measurements were performed on a LX20-Pro auto-analyser using dedicated kits (Beckman-Coulter, Woerden, The Netherlands). The interassay coefficients of variation (CV) were 3.3%, 2.1% and 2.0% at TC concentrations of 86.6, 165.9 and 227.0 mg/dl, respectively; 4.1%, 3.4% and 3.6% at HDL-cholesterol concentrations of 24.0, 46.4, and 63.8 mg/dl, respectively; 3.7%, 2.4% and 2.3% at LDL-cholesterol concentrations of 46.4, 68.8, and 103.3 mg/dl, respectively; 2.6% and 2.2% at TG concentrations of 109.8 and 147.9 mg/dl, respectively; 3.5% and 3.5% at ApoA concentrations of 88.0 and 140.0 mg/dl, respectively; and 3.3% and 2.9% at ApoB concentrations of 54.0 and 134.0 mg/dl, respectively. For technical reasons, 66% of case–control sets were not measured in the same analytical batch. However, batch to batch differences are considered to be minor: no significant between-day drift, time shifts or other trends were observed and the percentage of variance attributable to batch to batch differences varied between 0.25% and 1.65%.

Measurements of CRP,[24] C peptide[25] and HbA1c[26] have been described previously. ROM was measured by a spectrophotometric test that determines the concentration of hydroperoxides (ROOH) with a kit from Diacron, Italy (dROM). The interassay coefficients of variation were 5.3% and 4.7% at ROM concentrations of 174.0 and 487.0 U/ml, respectively.

For all analyses, laboratory technicians were blinded to the case–control status of the samples.

Statistical analysis

Differences in baseline characteristics between cases and controls were tested by the Wilcoxon two-sample test (continuous variables) or the χ^2 test (categorical variables). Lipid and lipoprotein characteristics of cases and controls were presented by fasting status; differences between cases and controls per fasting status category were tested by the Wilcoxon two-sample test and differences between controls over fasting status categories were tested by the Kruskal–Wallis test. The correlations of serum lipids and lipoproteins with dietary and lifestyle factors for control subjects were evaluated by Spearman partial correlation coefficients adjusted for age, sex and body mass index (BMI). The mean concentrations of serum lipids and lipoproteins were evaluated across categories of physical activity and smoking status for control subjects and a p for trend value was calculated using linear regression.

Incidence rate ratios (RRs[27]) and 95% CIs for the associations between serum lipids and lipoproteins (TC, HDL, LDL, TG, apoA, and apoB) and CRC or cancer subsites were estimated by conditional logistic regression analysis. In addition, ratios of lipids and lipoproteins (apoB/apoA, LDL/HDL, TC/HDL, TG/HDL and the atherogenic index of plasma (AIP; defined as the base 10 logarithm of the ratio TG/HDL[28])) were investigated. All data were analysed by quintiles with cut-off points based on the distribution in control subjects, and by continuous variables with an increment of 1SD. To test for trend across categories, the quintiles of lipids and lipoproteins were modelled as continuous variables in which each quintile was assigned the median value of controls in that quintile.

RR estimates were computed in a crude model, which was conditioned on the matching factors, and in a multivariate model with additional adjustments for potential confounders including height, weight, energy from fat and energy from non-fat, smoking habits (never smokers, former smokers who quit ≥20 years, former smokers who quit 10–20 years, former smokers who quit <10 years, currents smokers who smoke <15 cigarettes/day, current smokers who smoke 15–25 cigarettes/day, current smokers who smoke ≥25 cigarettes/day), smoking duration, physical activity (inactive, moderately inactive, moderately active, active),[29] education (none, primary school, technical/professional school, secondary school, longer education including university degree, not specified; as a proxy variable for socioeconomic status) and consumption of fruit, vegetables, red and processed meats, fish, fibre and alcohol (all in g/day). Waist circumference, waist to hip ratio, ever use of postmenopausal hormone therapy (women only), intake of cholesterol, total fat, saturated fat, monounsaturated fat, polyunsaturated fat and calcium were also examined but they did not materially change the effect estimates and were therefore not included in the final models. Risk estimates for HDL were adjusted for LDL and vice versa, but they did not materially change and were therefore not reported.

To evaluate whether preclinical disease may have influenced any of the results, additional analyses were conducted after exclusion of cases diagnosed within 2 years after recruitment and their matched controls (approximately 25% of the population).

The relevant models were further adjusted for (1) blood concentrations of CRP, HbA1c, C peptide and ROM (biomarkers of systemic inflammation, glucose exposure, pancreatic insulin secretion and oxidative stress, respectively); (2) waist circumference, blood pressure, diabetes mellitus, TG and HDL (the five factors of the metabolic syndrome according to the International Diabetes Federation[30]); or (3) all of the above variables. One dataset containing all available data was created which included only 235 colon case–control sets mainly due to the fact that HbA1c and C peptide levels were only assayed for part of the current dataset.

Possible heterogeneity of effects between age groups (in tertiles), sex, region (North: Norway, Sweden, Denmark; Middle: Netherlands, Germany, France, UK; South: Italy, Spain, Greece) and menopausal status (premenopausal/perimenopausal women vs (surgical) postmenopausal women) was tested using the heterogeneity statistic derived from the inverse variance method.

Effect modification (on the multiplicative scale) by several factors was tested by including a product term of these factors (in categories or tertiles) with the relevant lipids or lipoproteins (in tertiles) in the model. Potential effect modifiers included physical activity, smoking status, waist circumference, blood pressure, diabetes at baseline, metabolic syndrome and BMI, weight, hip, waist to hip ratio, alcohol use, insulin-like growth factor, CRP, HbA1c, C peptide and ROM. Joint effects of these potential effect modifiers with relevant lipid or lipoprotein concentrations were calculated, for which a combined reference category of the lowest category of the abovementioned factors with a low lipid or lipoprotein concentration was used.

All analyses were performed using SAS Software Version 9.1 (SAS Institute Inc). For all analyses, two-sided p values <0.05 were considered statistically significant.

RESULTS

CRC cancer cases were heavier, had a higher BMI, were less physically active and appeared to have a higher education than controls (table 1). Median concentrations of CRP and ROM were somewhat higher in cases than in controls.

Table 1 Description of colorectal cancer cases and matched controls

Baseline characteristic	Cases	Controls	p Value‡
Colorectal	1238	1238	
Colon	779	779	
Proximal	322	322	
Distal	381	381	
Unspecified	76	76	
Rectum	459	459	
Number of men	618	618	
Number of women	620	620	
Age*			
At recruitment	59.0 (53.7–63.0)	59.1 (53.7–63.0)	0.99
At blood donation	59.1 (53.8–63.1)	59.2 (53.9–63.0)	0.95
At end of follow-up	62.5 (57.8–67.0)		
Years of follow-up	3.8 (2.1–5.5)		
Anthropometrics*			
Height (cm)	167.5 (161.0–175.0)	167.4 (159.9–174.5)	0.07
Weight (kg)	74.5 (65.0–84.5)	72.8 (64.0–82.3)	<0.01
BMI (kg/m^2)	26.3 (23.8–29.1)	25.8 (23.7–28.4)	0.02
Smoking duration*	13.0 (0.0–33.0)	10.0 (0.0–32.0)	0.31
Other smoking habits†			
Never	508 (41.0)	531 (42.9)	0.79
Former smoker, time since quitting ≥20 years	162 (13.1)	168 (13.6)	
Former smoker, time since quitting ≥10 and <20 years	123 (9.9)	120 (9.7)	
Former smoker, time since quitting <10 years	109 (8.8)	94 (7.6)	
Smoker, cigarettes per day <15	118 (9.5)	120 (9.7)	
Smoker, cigarettes per day ≥15 and <25	99 (8.0)	104 (8.4)	
Smoker, cigarettes per day ≥25	29 (2.3)	29 (2.3)	
Missing/unspecified smoking status	90 (7.3)	72 (5.8)	
Physical activity†			
Inactive	304 (24.6)	283 (22.9)	0.06
Moderately inactive	368 (29.7)	343 (27.7)	
Moderately active	262 (21.2)	243 (19.6)	
Active	232 (18.7)	288 (23.3)	
Missing/unspecified	72 (5.8)	81 (6.5)	
Highest educational level†			
None	60 (4.9)	53 (4.3)	0.06
Primary school	417 (33.7)	477 (38.5)	
Technical/professional school	311 (25.1)	307 (24.8)	
Secondary school	192 (15.5)	152 (12.3)	
Longer education (including university degree)	219 (17.7)	220 (17.8)	
Missing/unspecified	39 (3.2)	29 (2.3)	
Fasting status†			
Not fasting	599 (48.4)	604 (48.8)	0.99
In between	287 (23.2)	284 (22.9)	
Fasting	329 (26.6)	329 (26.6)	
Missing	23 (1.9)	21 (1.7)	
Menopausal status (only women)†			
Premenopausal	63 (10.2)	64 (10.3)	1.00
Perimenopausal	77 (12.4)	76 (12.3)	
Postmenopausal (natural)	450 (72.6)	449 (72.4)	
Surgical postmenopausal	30 (4.8)	31 (5.0)	
HRT use (only women)†			
No	446 (71.9)	456 (73.6)	0.81
Yes	150 (24.2)	141 (22.7)	
Missing	24 (3.9)	23 (3.7)	
Dietary variables*			
Fruit intake (g/day)	184.3 (98.6–308.2)	192.5 (108.1–315.9)	0.14
Vegetable intake (g/day)	153.8 (99.0–231.4)	156.2 (101.8–238.4)	0.37
Alcohol (g/day)	9.0 (1.4–24.1)	8.2 (1.6–21.6)	0.27
Red meat (g/day)	49.0 (26.4–78.7)	48.3 (25.6–76.7)	0.34
Processed meat (g/day)	26.3 (13.8–43.7)	25.2 (13.0–44.6)	0.23
Fish (g/day)	26.3 (13.9–46.1)	28.5 (13.8–49.3)	0.15
Energy from fat (kcal)	711.3 (546.8–913.2)	713.0 (555.6–890.7)	0.96

Continued

Table 1 Continued

Baseline characteristic	Cases	Controls	p Value‡
Energy from non-fat (kcal)	1363.9 (1096.3–1661.4)	1329.9 (1087.8–1618.0)	0.16
Total fibre intake (g/day)	21.8 (17.2–27.4)	22.4 (17.8–27.3)	0.11
Total fat intake (g/day)	79.0 (60.8–101.5)	79.2 (61.7–99.0)	0.96
Other biomarkers*			
CRP (mg/l)	2.8 (1.1–5.1)	2.3 (1.1–4.5)	<0.01
C peptide (ng/ml)	4.0 (2.9–6.1)	3.9 (2.7–5.8)	0.08
HbA1c (%)	5.7 (5.5–6.0)	5.7 (5.5–6.0)	0.05
ROM (U/ml)	396.0 (347.0–444.0)	380.0 (332.0–426.0)	<0.01

*Values are median (IQR).
†Values are n (%).
‡Calculated using Wilcoxon two-sample test for continuous variables and χ^2 tests for categorical variables.
BMI, body mass index; CRP, C reactive protein; HbA1c, glycosylated haemoglobin; HRT, postmenopausal hormone therapy; ROM, reactive oxygen metabolites.

Blood concentrations of most lipids and lipoproteins among controls were similar for non-fasting, in between and fasting subjects, with the exception of serum concentrations of TC and TG which were statistically significantly lower for fasting subjects (table 2). HDL concentrations were statistically significantly different between cases and controls in fasting subjects (table 2).

When Spearman partial correlation coefficients were calculated between lipids and lipoproteins, TC was highly correlated with LDL (ρ=0.88) and apoB (ρ=0.88); HDL was highly correlated with apoA (ρ=0.92); and LDL was highly correlated with apoB (ρ=0.94; all p<0.01; data not shown). All other correlation coefficients between lipids and lipoproteins were between −0.44 and 0.38. Most correlations between serum lipids/lipoproteins and biomarkers were weak (range ρ=−0.23 to 0.35), and those between serum lipids/lipoproteins and dietary/lifestyle factors were very weak (range ρ=−0.17 to 0.18). Higher Spearman partial correlation coefficients were observed between BMI and HDL (ρ=−0.24), BMI and TG (ρ=0.26), alcohol use and HDL-cholesterol (ρ=0.20) and alcohol use and apoA (ρ=0.24; all p<0.01; data not shown). The mean concentrations of HDL and apoA increased with increasing degrees of physical activity (p for trend <0.01). The concentrations of HDL and apoA decreased from categories of never to former to current smokers (p for trend <0.01 and 0.02, respectively), whereas the concentrations of TG increased with these categories (p for trend <0.01).

Concentrations of TC, HDL and apoA were inversely associated with CRC risk, which were particularly observed for colon cancer risk but not for rectal cancer risk (table 3). Although the risk estimates for proximal colon cancer were slightly weaker (RR for 1 SD increase 0.82 (95% CI 0.65 to 1.03) for HDL and 0.86 (95% CI 0.68 to 1.07) for apoA; data not shown), inverse patterns for HDL and apoA were only (borderline) statistically significantly shown for distal colon cancer risk (0.79 (95% CI 0.65 to 0.96) for HDL and 0.83 (95% CI 0.69 to 1.01) for apoA; data not shown).

When lipid ratios in relation to cancer risk were investigated, only AIP in relation to colon cancer risk showed consistent results for both the categorical as well as the continuous analyses (see table 1 in online supplement). These results are probably driven by HDL as this lipid ratio has HDL in its denominator.

Of the abovementioned associations, only the associations between HDL and CRC and colon cancer risk remained statistically significant (RR for 1 SD increase 0.86 (95% CI 0.76 to 0.97) and 0.80 (95% CI 0.69 to 0.93), respectively) after exclusion of the first 2 years of follow-up.

The final model of the most relevant association between HDL and colon cancer risk was further adjusted for several biomarkers and/or the four factors of the metabolic syndrome other than HDL, but this did not substantially alter the risk estimates (table 4).

No heterogeneity of the association between HDL and colon cancer risk was observed by age (p=0.49), sex (p=0.45), region (p=0.98) or menopausal status (p=0.86). The association between HDL and colon cancer risk also did not vary by any of the tested potential effect modifiers, with the exception of

Table 2 Serum analyte characteristics of colorectal cancer cases and matched controls by fasting status

	Not fasting			In between			Fasting			
	Cases	Controls	p Value†	Cases	Controls	p Value†	Cases	Controls	p Value†	p Value‡
Total number of subjects	599	604		287	284		329	329		
Serum analytes*										
Total cholesterol (mg/dl)	247.5 (216.2 to 280.7)	250.6 (222.0 to 283.5)	0.14	247.5 (220.8 to 279.2)	251.4 (226.6 to 284.6)	0.47	234.7 (206.5 to 266.4)	240.5 (211.9 to 269.9)	0.18	<0.01
HDL- cholesterol (mg/dl)	54.5 (44.5 to 65.7)	55.3 (45.6 to 68.4)	0.07	54.1 (44.5 to 67.7)	53.8 (45.2 to 67.3)	0.96	52.6 (42.2 to 63.4)	54.1 (45.6 to 63.8)	0.03	0.57
LDL- cholesterol (mg/dl)	162.4 (133.8 to 189.1)	161.6 (136.1 to 194.1)	0.40	163.6 (137.3 to 191.0)	164.7 (143.2 to 190.6)	0.50	161.3 (137.7 to 188.3)	167.0 (139.6 to 193.4)	0.14	0.58
Triglycerides (mg/dl)	146.1 (100.1 to 211.7)	140.8 (96.5 to 200.2)	0.12	138.2 (94.8 to 201.9)	138.2 (99.2 to 192.2)	0.98	98.3 (67.0 to 139.9)	94.8 (70.0 to 135.5)	0.45	<0.01
Apolipoprotein A-1 (mg/dl)	172.0 (151.0 to 193.0)	174.0 (155.0 to 194.0)	0.23	173.0 (152.0 to 201.0)	174.0 (150.0 to 198.0)	0.52	167.0 (147.0 to 187.0)	170.0 (150.0 to 189.0)	0.10	0.18
Apolipoprotein B (mg/dl)	120.0 (101.0 to 139.0)	119.0 (101.0 to 138.0)	0.59	120.0 (104.0 to 137.0)	121.0 (105.0 to 139.0)	0.65	117.0 (102.0 to 133.0)	118.0 (102.0 to 133.0)	0.64	0.23

*Values are median (IQR).
†p Value for difference between cases and controls per fasting status category calculated using the Wilcoxon two-sample test.
‡p Value for difference between controls over fasting status categories calculated using the Kruskal–Wallis test.

Table 3 Serum lipid and lipoprotein concentrations and colorectal cancer risk by site

Serum analytes	Quintiles* Q1	Q2	Q3	Q4	Q5	p_{trend} (median)	Continuous† For every SD increase
	Colorectal cancer						
Total cholesterol							
N cases/controls	223/190	219/195	179/191	176/199	178/200		975/975
Crude RR	1.00	0.99 (0.77 to 1.26)	0.83 (0.65 to 1.07)	0.83 (0.64 to 1.06)	0.78 (0.60 to 1.01)	0.03	0.95 (0.87 to 1.03)
Adjusted RR‡	1.00	0.90 (0.68 to 1.20)	0.78 (0.58 to 1.05)	0.74 (0.55 to 1.00)	0.68 (0.50 to 0.92)	<0.01	0.92 (0.84 to 1.01)
HDL-cholesterol							
N cases/controls	226/178	182/189	169/171	228/210	161/218		966/966
Crude RR	1.00	0.79 (0.62 to 1.01)	0.78 (0.60 to 1.01)	0.89 (0.69 to 1.14)	0.65 (0.49 to 0.86)	0.02	0.87 (0.80 to 0.95)
Adjusted RR‡	1.00	0.75 (0.56 to 1.01)	0.78 (0.57 to 1.07)	0.85 (0.62 to 1.15)	0.54 (0.39 to 0.77)	<0.01	0.83 (0.74 to 0.93)
LDL-cholesterol							
N cases/controls	207/196	208/200	210/190	183/190	162/194		970/970
Crude RR	1.00	1.00 (0.78 to 1.28)	1.01 (0.79 to 1.30)	0.87 (0.68 to 1.13)	0.82 (0.63 to 1.07)	0.09	0.95 (0.88 to 1.03)
Adjusted RR‡	1.00	0.94 (0.71 to 1.25)	1.02 (0.76 to 1.37)	0.86 (0.64 to 1.16)	0.73 (0.54 to 0.99)	0.04	0.93 (0.84 to 1.02)
Triglycerides							
N cases/controls	168/194	210/192	169/189	181/180	211/184		939/939
Crude RR	1.00	1.23 (0.95 to 1.60)	1.01 (0.77 to 1.33)	1.15 (0.88 to 1.52)	1.30 (0.98 to 1.72)	0.14	1.08 (0.99 to 1.18)
Adjusted RR‡	1.00	1.28 (0.95 to 1.73)	1.02 (0.74 to 1.41)	1.17 (0.85 to 1.63)	1.19 (0.84 to 1.69)	0.62	1.03 (0.92 to 1.15)
Apolipoprotein A-1							
N cases/controls	196/167	194/175	171/193	211/203	180/214		952/952
Crude RR	1.00	0.95 (0.74 to 1.22)	0.86 (0.66 to 1.12)	0.95 (0.73 to 1.24)	0.78 (0.59 to 1.04)	0.11	0.92 (0.84 to 1.00)
Adjusted RR‡	1.00	0.92 (0.68 to 1.25)	0.73 (0.53 to 1.01)	0.84 (0.61 to 1.16)	0.67 (0.48 to 0.95)	0.02	0.87 (0.79 to 0.97)
Apolipoprotein B							
N cases/controls	185/185	209/192	178/190	194/202	184/181		950/950
Crude RR	1.00	1.14 (0.88 to 1.48)	0.97 (0.75 to 1.26)	1.06 (0.81 to 1.37)	1.04 (0.79 to 1.36)	0.95	1.02 (0.94 to 1.11)
Adjusted RR‡	1.00	1.05 (0.77 to 1.42)	0.93 (0.69 to 1.27)	0.93 (0.69 to 1.27)	0.94 (0.68 to 1.30)	0.51	0.99 (0.90 to 1.09)
	Colon cancer						
Total cholesterol							
N cases/controls	146/124	139/124	118/120	100/124	114/125		617/617
Adjusted RR‡	1.00	0.88 (0.61 to 1.26)	0.80 (0.55 to 1.15)	0.66 (0.44 to 0.98)	0.66 (0.45 to 0.98)	0.02	0.88 (0.78 to 1.00)
HDL-cholesterol							
N cases/controls	152/107	112/117	112/112	146/132	90/144		612/612
Adjusted RR‡	1.00	0.72 (0.49 to 1.06)	0.73 (0.49 to 1.10)	0.83 (0.56 to 1.22)	0.42 (0.28 to 0.65)	<0.01	0.78 (0.68 to 0.89)
LDL-cholesterol							
N cases/controls	125/120	137/140	130/113	121/120	101/121		614/614
Adjusted RR‡	1.00	0.86 (0.60 to 1.24)	1.04 (0.71 to 1.53)	0.91 (0.61 to 1.34)	0.72 (0.48 to 1.08)	0.17	0.92 (0.81 to 1.05)
Triglycerides							
N cases/controls	103/122	144/134	103/126	110/110	131/90		591/591
Adjusted RR‡	1.00	1.30 (0.88 to 1.92)	0.95 (0.62 to 1.45)	1.17 (0.73 to 1.79)	1.42 (0.91 to 2.31)	0.23	1.08 (0.93 to 1.26)
Apolipoprotein A-1							
N cases/controls	128/98	128/114	111/121	104/138	104/138		600/600
Adjusted RR‡	1.00	0.93 (0.62 to 1.40)	0.75 (0.50 to 1.15)	0.80 (0.53 to 1.19)	0.57 (0.37 to 0.88)	<0.01	0.82 (0.72 to 0.94)
Apolipoprotein B							
N cases/controls	121/121	127/121	113/119	119/126	119/112		599/599
Adjusted RR‡	1.00	1.03 (0.69 to 1.53)	0.91 (0.61 to 1.36)	0.90 (0.60 to 1.34)	0.99 (0.64 to 1.52)	0.74	1.00 (0.88 to 1.15)
	Rectal cancer						
Total cholesterol							
N cases/controls	77/66	80/71	61/71	76/75	64/75		358/358
Adjusted RR‡	1.00	0.92 (0.57 to 1.51)	0.67 (0.39 to 1.14)	0.84 (0.51 to 1.38)	0.68 (0.41 to 1.13)	0.13	0.97 (0.83 to 1.12)
HDL-cholesterol							
N cases/controls	74/71	70/72	57/59	82/78	71/74		354/354
Adjusted RR‡	1.00	0.83 (0.51 to 1.36)	0.88 (0.51 to 1.54)	0.92 (0.54 to 1.58)	0.79 (0.42 to 1.49)	0.59	0.94 (0.76 to 1.15)
LDL-cholesterol							
N cases/controls	82/76	71/60	80/77	62/70	61/73		356/356
Adjusted RR‡	1.00	1.15 (0.71 to 1.88)	1.05 (0.66 to 1.69)	0.77 (0.48 to 1.25)	0.79 (0.48 to 1.29)	0.14	0.94 (0.81 to 1.09)
Triglycerides							
N cases/controls	65/72	66/58	66/63	71/70	80/85		348/348
Adjusted RR‡	1.00	1.38 (0.81 to 2.33)	1.41 (0.81 to 2.47)	1.30 (0.74 to 2.29)	1.06 (0.60 to 1.88)	0.70	0.97 (0.81 to 1.16)
Apolipoprotein A-1							
N cases/controls	68/69	66/61	60/72	82/74	76/76		352/352
Adjusted RR‡	1.00	0.98 (0.61 to 1.59)	0.76 (0.45 to 1.27)	0.97 (0.55 to 1.68)	0.84 (0.46 to 1.54)	0.57	0.96 (0.78 to 1.17)

Continued

Table 3 Continued

Serum analytes	Quintiles* Q1	Q2	Q3	Q4	Q5	p_{trend} (median)	Continuous† For every SD increase
Apolipoprotein B							
N cases/controls	64/64	82/71	65/71	75/76	65/69		351/351
Adjusted RR‡	1.00	1.25 (0.76 to 2.06)	0.96 (0.58 to 1.59)	1.07 (0.65 to 1.76)	0.95 (0.57 to 1.59)	0.64	0.99 (0.85 to 1.16)

*Quintile cut-off points were the same for all cancer sites. Total cholesterol: 211.5, 237.8, 259.5, 287.7 mg/dl; HDL-cholesterol: 43.3, 51.0, 58.8, 70.4 mg/dl; LDL-cholesterol: 131.9, 155.1, 175.2, 201.5 mg/dl; triglycerides: 79.7, 110.7, 145.3, 201.9 mg/dl; apolipoprotein A-1: 148.0, 165.0, 180.0, 202.0 mg/dl; apolipoprotein B: 98.0, 113.0, 125.0, 142.0 mg/dl.
†Increases in 1 SD were the same for all cancer sites. Total cholesterol: 46.8 mg/dl; HDL-cholesterol: 16.6 mg/dl; LDL-cholesterol: 41.8 mg/dl; triglycerides: 104.5 mg/dl; apolipoprotein A-1: 32.0 mg/dl; apolipoprotein B: 27.0 mg/dl.
‡Conditioned on matching factors and adjusted for height, weight, smoking habits, physical activity, education, consumption of fruit, vegetables, meat, fish and alcohol, intake of fibre, energy from fat and energy from non-fat.
HDL, high density lipoprotein; LDL, low density lipoprotein.

weight for which a statistically significant interaction effect was observed (p=0.05).

Although no clear patterns were observed for the joint effects, it appeared that the effect of HDL on colon cancer risk was mostly seen in the highest category of the risk factor (eg, the inverse association of HDL with colon cancer risk was most apparent in the most obese persons; data not shown). In addition, the effect of the risk factor on colon cancer risk was mostly seen in the lowest category of HDL (eg, the effect of weight on colon cancer risk was most apparent in persons with the lowest concentrations of HDL; data not shown).

DISCUSSION

In this study, the largest CRC study to date and one of the first based on European populations, the results indicated that prediagnostic concentrations of HDL and its component apoA are inversely statistically significantly associated with CRC risk. For both biomarkers, the observed association was limited to the colon anatomical subsite, but only the association with HDL remained after exclusion of the first 2 years of follow-up. Further adjustments for biomarkers involved in potential mechanistic pathways did not change any of the risk estimates.

The relation between HDL concentrations and CRC risk has been previously investigated in three other prospective cohort studies, two based on North American populations[6 7] and one on a Finnish[31] population. In the Atherosclerosis Risk in Communities (ARIC) study with 194 cases of CRC, the RR of a low HDL concentration (<35 mg/dl for men and <45 mg/dl for women) compared with a high HDL concentration was 1.19 (95% CI 0.9 to 1.6).[6] In the Cardiovascular Health cohort study with 102 cases of CRC, a RR of 0.9 (95% CI 0.7 to 1.0) per quartile of increased HDL concentration was observed.[7] The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study with 507 cases of CRC observed relative risks of 0.99 (95% CI 0.76 to 1.30), 0.73 (95% CI 0.55 to 0.98), 0.85 (95% CI 0.64 to 1.14) and 1.01 (95% CI 0.76 to 1.35) for increasing quintiles of HDL concentrations.[31] In these studies, a small population size was probably a limiting factor for the lack of statistical significance, but it is of interest that the direction of the findings (at least in the first two studies) is very similar to those observed in the present study.

Table 4 Additional adjustments for association between HDL-cholesterol and colon cancer risk

Model	Continuous¶ Per 1 SD increase
Adjusted*	0.78 (0.68 to 0.89)
Adjusted†	0.77 (0.61 to 0.97)
Adjusted† + all biomarkers‡	0.80 (0.62 to 1.02)
Adjusted† + 4 factors metabolic syndrome§	0.75 (0.59 to 0.97)
Adjusted† + all biomarkers‡ + 4 factors metabolic syndrome§	0.77 (0.59 to 1.00)

*Conditioned on matching factors and adjusted for height, weight, smoking habits, physical activity, education, consumption of fruit, vegetables, meat, fish and alcohol, intake of fibre, energy from fat and energy from non-fat; N cases/controls=612/612.
†Conditioned on matching factors and adjusted for height, weight, smoking habits, physical activity, education, consumption of fruit, vegetables, meat, fish and alcohol, intake of fibre, energy from fat and energy from non-fat; after removing all cases and controls with missing data for the additional confounders; N cases/controls=235/235.
‡Included in 'all biomarkers' are blood concentrations of C reactive protein, glycosylated haemoglobin, C peptide and reactive oxygen metabolites.
§Included in '4 factors metabolic syndrome' are waist circumference, triglycerides, blood pressure and diabetes mellitus.
¶Increases in 1 SD in HDL-cholesterol were 16.6 mg/dl.

The small size of the three studies also did not permit differentiation between the colon and rectum anatomical subsites. There is accumulating evidence that subsites of the colorectum have different aetiologies.[32–36] The present results suggest that the inverse association of cancer risk observed with HDL is more strongly present in the colon rather than in the rectum. When colon cancers were further subdivided into proximal and distal colon cancers, the risk estimates for both of these subsites were <1, but only those for distal colon cancer were statistically significant. Although this difference may be due to a limited number of cases in the proximal colon cancer analyses (251 proximal vs 305 distal cancer cases), the association between HDL and specific anatomical subsites within the colorectum should be further examined.

There are several possible mechanisms by which blood concentrations of HDL-cholesterol may be directly or indirectly involved in colorectal carcinogenesis. Decreased concentrations of HDL have been related to increased circulating concentrations of proinflammatory cytokines such as interleukin 6 (IL-6) and tumour necrosis factor-α receptors,[10] whereas increased concentrations of anti-inflammatory cytokines such as IL-10 are associated with raised concentrations of HDL-cholesterol.[10] These proinflammatory cytokines seem to stimulate cell growth and cellular proliferation and inhibit apoptosis,[37] whereas anti-inflammatory cytokines inhibit the production of these proinflammatory cytokines.[38] These observations suggest that HDL may modulate colon carcinogenesis through inflammatory pathways. Another proposed pathway is through modulation of oxidative stress because HDL displays antioxidative activities and is believed to confer protection against oxidation of LDL-cholesterol.[12 13] A low concentration of HDL leads to more oxidised LDL-cholesterol, which has been described as a cause of increased intracellular oxidative stress,[39] a process that is involved in the pathogenesis of cancer.[40] Low HDL is also a characteristic feature of insulin resistance,[11] which has also been hypothesised to play a role in the aetiology of CRC.[41] In the present study, however, the inverse association between HDL and colon cancer risk remained unchanged when the results were adjusted for biomarkers involved in these potential mechanistic pathways. In addition, the association between HDL and colon cancer risk did

not vary by any of these biomarkers and the joint effects analysis suggested that the association is largely independent of the other biomarkers, particularly in their highest category. This may be due to measurement error in the determination of blood concentrations of the other biomarkers, which may lead to incomplete adjustment. On the other hand, it may suggest that the association between HDL and colon cancer risk reflects another mechanistic pathway which we did not investigate. Nevertheless, the possibility that a low concentration of HDL by itself is a true risk factor for colon cancer cannot be excluded by our findings. Therefore, it still remains to be established whether low HDL concentrations are just correlated with other truly detrimental pathways, whether they are intermediate factors in the colon carcinogenic process or are a true risk factor initiating a mechanistic path on the road to colon cancer.

Interestingly, we were not able to show a robust association between other blood lipid concentrations and CRC. Although this may be due to the possibility that no association exists, it may also be explained by the increasing use of lipid-lowering drugs (eg, statins) and low-dose aspirin in patients with deviant blood lipid concentrations. Both drugs have been associated with a chemopreventive effect on colorectal carcinogenesis[42 43] and may thus interfere with the associations investigated in this study. Unfortunately, we do not have access to all medical files of included subjects and the exact influence of this medication on our findings therefore remains uncertain.

The main strengths of this study are its prospective design, the relatively large sample size and the use of pre-diagnostic measurements of blood lipids and lipoproteins. Moreover, this study is based on countries from the north to the south of Europe, spanning a wide range of dietary consumptions, many different lifestyle patterns and of CRC incidence.

A limitation of this study is that only a single baseline measurement of lipids and lipoproteins was used. However, Al-Delaimy *et al* investigated the reliability of blood lipids and lipoproteins in the two Dutch cohorts within EPIC at two time points several years apart. They concluded that these biomarkers were suitable for use in cohort studies because the ranking of study subjects according to their biomarker exposure was sufficiently accurate.[23] Several variables were used to match controls to CRC cases. If too many characteristics are used, overmatching may occur which leads to a situation where the compared groups will resemble each other too much and the effect between the determinant and the outcome will be diluted. If it did, the true underlying inverse association between HDL and colon cancer risk would have been even more pronounced than observed. While the size of the current study is large in comparison with other prospective studies on the same topic, it may still be limited for consideration of effect modification by other factors. In addition, the relatively short follow-up period (3.8 years) of our study is a disadvantage. Cases that were diagnosed shortly after the start of the study may already have had abdominal complaints which may have resulted in changes in their dietary or lifestyle habits and subsequently changed their lipid or lipoprotein concentration in the blood. Or the presence of the tumour, although not yet diagnosed, may itself lead to changes in lipid metabolism. When the first 2 years of follow-up were excluded, the risk estimates for some relations turned out to be only marginally weaker but lost statistical significance. This may have been due to the fact that the numbers in our analyses decreased in such a way that the power to detect an effect was too low. However, it may also indicate that reverse causality did occur in our study, which is why prospective studies like this one are particularly important. Nevertheless, since the development of CRC is a long-term process, our results—which are based on a relatively short follow-up time—should be interpreted with caution. In the future, a longer period of follow-up in EPIC may be necessary to rule out any effect of reverse causality.

In conclusion, our findings show that high concentrations of serum HDL are associated with a lower risk of colon cancer. Further investigations are needed to clarify the exact role of HDL in colon carcinogenesis.

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Acknowledgements The authors thank P Beekhof and H Cremers for the biomarker measurements of lipids and lipoproteins.

Funding This work was supported by the European Commission: Public Health and Consumer Protection Directorate 1993-2004; Research Directorate-General 2005-.; Ligue contre le Cancer, Societé 3M, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center, Federal Ministry of Education and Research (Germany); Danish Cancer Society (Denmark); Health Research Fund (FIS) of the Spanish Ministry of Health, The participating regional governments and institutions (Spain); Cancer Research UK, Medical Research Council (UK); Hellenic Ministry of Health, the Stavros Niarchos Foundation and the Hellenic Health Foundation (Greece); Italian Association for Research on Cancer, National Research Council (Italy); Dutch

Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); Swedish Cancer Society, Swedish Scientific Council, Regional government of Västerbotten (Sweden); Norwegian Cancer Society (Norway).

Competing interests The institution of FvD has received grants from the Ministry of Public Health, Welfare and Sports for the submitted work. The institution of HBBdM has received grants from the Ministry of Public Health, Welfare and Sports for the submitted work. The institution of TP has received grants from German Cancer Aid, Federal Ministry for Education and Research, European Union for the submitted work. The institution of RT has received support from the European Union and AIRC-ITALY for the submitted work. The institution of DD has received grants from German Cancer Aid, Federal Ministry for Education and Research, European Union for the submitted work. The institution of AT has received grants from Stavros Niarchos Foundation for the submitted work. The institution of PL has received grants from the Hellenic Ministry of Health for the submitted work. The institution of VD has received grants from the Hellenic Health Foundation for the submitted work. The institution of K-TK has received grants from MRC and Cancer Research UK for the submitted work. There are no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval This study was conducted with the approval of the ethics review boards of the International Agency for Research on Cancer and individual EPIC centres. EPIC participants provided written consent for the use of their blood samples and all data.

Provenance and peer review Not commissioned; externally peer reviewed.

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Gut 2011 60: 1094-1102 originally published online March 7, 2011
doi: 10.1136/gut.2010.225011