

# Prediagnostic Total and High-Density Lipoprotein Cholesterol and Risk of Cancer

Jiyoung Ahn,<sup>1</sup> Unhee Lim,<sup>1</sup> Stephanie J. Weinstein,<sup>1</sup> Arthur Schatzkin,<sup>1</sup> Richard B. Hayes,<sup>1</sup> Jarmo Virtamo,<sup>2</sup> and Demetrius Albanes<sup>1</sup>

<sup>1</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland, and <sup>2</sup>Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland

## Abstract

**Background:** Circulating total cholesterol has been inversely associated with cancer risk; however, the role of reverse causation and the associations for high-density lipoprotein (HDL) cholesterol have not been fully characterized. We examined the relationship between serum total and HDL cholesterol and risk of overall and site-specific cancers among 29,093 men in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort.

**Methods:** Fasting serum total and HDL cholesterol were assayed at baseline, and 7,545 incident cancers were identified during up to 18 years of follow-up. Multivariable proportional hazards models were conducted to estimate relative risks (RR).

**Results:** Higher serum total cholesterol concentration was associated with decreased risk of cancer overall (RR for comparing high versus low quintile, 0.85; 95% confidence interval, 0.79-0.91; *P* trend <0.001; >276.7 versus <203.9 mg/dL), and the inverse association was par-

ticularly evident for cancers of the lung and liver. These associations were no longer significant, however, when cases diagnosed during the first 9 years of follow-up were excluded. Greater HDL cholesterol was also associated with decreased risk of cancer (RR for high versus low quintile, 0.89; 95% confidence interval, 0.83-0.97; *P* trend = 0.01; >55.3 versus <36.2 mg/dL). The inverse association of HDL cholesterol was evident for cancers of lung, prostate, liver, and the hematopoietic system, and the associations of HDL cholesterol with liver and lung cancers remained after excluding cases diagnosed within 12 years of study entry.

**Conclusion:** Our findings suggest that prior observations regarding serum total cholesterol and cancer are largely explained by reverse causation. Although chance and reverse causation may explain some of the inverse HDL associations, we cannot rule out some etiologic role for this lipid fraction. (Cancer Epidemiol Biomarkers Prev 2009;18(11):2814-21)

## Introduction

Population-based studies have reported that greater circulating total cholesterol concentration is associated with decreased cancer mortality (1-11) and incidence (10, 12-14). However, it is unclear whether the observed association is causal or due to an effect of preclinical disease on serum levels (i.e., through metabolic depression or increased utilization of cholesterol during carcinogenesis; ref. 15). One prospective study showed that the cholesterol-cancer association was present for serum determinations made 6 or more years before the diagnosis of cancer (16). By contrast, another study observed an inverse total cholesterol-cancer mortality relationship that weakened with longer follow-up, although it did not disappear completely (11), and they (11) and others (17) reported that total cholesterol concentrations decreased ~5 years before cancer death and 2 years before cancer diagnosis, respectively.

High-density lipoprotein (HDL) cholesterol could play a role in carcinogenesis through its influence on cell cycle entry, via a mitogen-activated protein kinase-dependent pathway (18), or regulation of apoptosis (19). We previously observed that greater circulating HDL cholesterol concentration was associated with decreased risk of non-Hodgkin lymphoma and that the inverse association was strongest during the first 4 to 6 years of follow-up (20), indicating that low concentration may serve as a marker of lymphoma. Other prospective studies reported inverse associations of HDL cholesterol with risks of breast cancer (21, 22) and lung cancer (23). Whether the observed inverse associations are causal or due to preclinical effects of malignancies remain unclear, however, and little is known regarding whether HDL cholesterol is associated with risk of other cancers or cancer overall.

In the present study, we prospectively examine the associations of serum total and HDL cholesterol with site-specific and overall cancer incidence among 29,093 male Finnish smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort.

## Materials and Methods

**Study Population.** The ATBC Study was a placebo-controlled, double-blinded primary prevention trial with a 2 × 2 factorial design that tested the hypothesis of

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**Requests for reprints:** Demetrius Albanes, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, EPS-3044, Bethesda, MD 20892. E-mail: daa@nih.gov

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whether  $\alpha$ -tocopherol or  $\beta$ -carotene supplementation would reduce the incidence of lung or other cancers in male smokers. Study rationale, design, and methods have been previously described (24). Between 1985 and 1988, 29,133 eligible men ages 50 to 69 years in southwestern Finland who smoked at least five cigarettes per day were randomized to receive supplements (50 mg/d of  $\alpha$ -tocopheryl acetate, 20 mg/d of  $\beta$ -carotene, or both) or a placebo. Exclusion criteria included history of cancer other than nonmelanoma skin cancer or carcinoma *in situ*; severe angina pectoris; chronic renal insufficiency; liver cirrhosis; chronic alcoholism; anticoagulant therapy; other medical problems that might have limited long-term participation; or current use of vitamin E (>20 mg/d), vitamin A (>20,000 IU/d), or  $\beta$ -carotene (>6 mg/d) supplements. After further excluding men with missing values of total cholesterol or HDL cholesterol ( $n = 40$ ), the analytic cohort included 29,093 men. The trial ended on April 30, 1993, and follow-up continued after randomization for the present study until diagnosis, death, or through March 31, 2003. The ATBC Study was approved by the institutional review boards of both the U.S. National Cancer Institute and the Finnish National Public Health Institute. All study participants provided written informed consent before the study initiation.

**Cohort Follow-up and Identification of Cases.** Incident cancer cases ( $n = 7,545$ ) were ascertained between April 1985 and March 31, 2003, by linkage of the cohort participants to the Finnish Cancer Registry, which provides ~100% cancer diagnosis for nationwide coverage (25). The medical records of all potential cancer cases diagnosed during the active ATBC Study trial and early post-intervention period through April 1999 were collected from the hospitals and pathology laboratories and reviewed by one or two study physicians. In addition, one or two study pathologists reviewed the histopathologic and cytologic specimens for these cancers. For cases diagnosed during the later passive follow-up period (i.e., May 1999–March 2003), case ascertainment has been provided by the Finnish Cancer Registry. In this report, we include results for cancers of lung, prostate, bladder, colorectum (excluding cancers of anal canal), stomach, kidney, pancreas (excluding endocrine tumors), hematopoietic system, larynx, liver, brain, melanoma, esophagus, and other cancers combined. *In situ*/benign cases were excluded.

**Baseline Data Collection.** During the baseline study visit, the men completed questionnaires regarding general characteristics and medical, smoking, and dietary histories. Diet was assessed using a 276-item food frequency questionnaire that queried frequency and portion size of food items consumed during the previous year (26). Trained study staff measured height and weight, which were used to calculate body mass index (BMI; weight divided by height squared,  $\text{kg}/\text{m}^2$ ) as an indicator of obesity, and diastolic and systolic blood pressure using a standard protocol (27).

**Serum Lipids.** At baseline, the participants also provided an overnight fasting blood sample, and serum specimens were stored at  $-70^\circ\text{C}$  (28). Cholesterol concentrations were determined enzymatically (CHOD-PAP method, Boehringer Mannheim). HDL cholesterol was measured after precipitation of very-low-density lipoprotein and low-density lipoprotein (LDL) cholesterol

with dextran sulfate and magnesium chloride. Baseline serum cholesterol levels were successfully analyzed in 29,093 men (99.9%). At the 3rd-year visit, 22,833 participants had an additional fasting blood collection, which was also analyzed for total and HDL cholesterol.

**Statistical Analysis.** Person-time was calculated from the date of randomization to the date of cancer diagnosis, death, or March 31, 2003, whichever came first. Absolute rates of cancer were standardized to the age distribution of person-years experienced by all study participants using 5-year age categories. We used Cox proportional hazard regression analysis to generate relative risks (RR) and 95% confidence intervals (95% CI) using the SAS PROC PHREG procedure, with age as the underlying time metric. Men were categorized by quintile of total cholesterol and HDL cholesterol. The multivariate model was adjusted for the following potential confounders (modeled as quintiles, unless otherwise indicated): age (continuous), intervention ( $\alpha$ -tocopheryl acetate and  $\beta$ -carotene supplementation, yes/no), level of education (elementary school or less, up to junior high school, high school or more), systolic blood pressure, BMI, physical activity, duration of smoking, number of cigarettes smoked per day, saturated fat intake (per 1,000 kcal intake of total energy), polyunsaturated fat intake (per 1,000 kcal intake of total energy), alcohol consumption, serum total cholesterol (for HDL cholesterol model only), and serum HDL cholesterol (for total cholesterol model only). Tests for linear trend were conducted by treating the median values of each exposure category as a single continuous variable in the model. We also applied nonparametric regression using cubic splines (29) to examine the association of total and HDL cholesterol with cancer risk, and conducted lag analyses that excluded cases diagnosed within up to 15 years of follow-up. In addition, stratified analyses were done by BMI, physical activity, blood pressure, alcohol consumption, and smoking. We formally tested for interactions using log-likelihood ratio tests. All analyses were conducted using SAS, version 9.1, software (SAS Institute, Inc.). All statistical tests were two-sided.

## Results

Average total and HDL cholesterol values for the study population at baseline were 241.2 mg/dL (SD 45.1) and 46.3 mg/dL (SD 12.3), respectively. Pearson correlations between the baseline and 3-year measurements for total and HDL cholesterol were high ( $r = 0.74$  and  $r = 0.77$ , respectively). Total cholesterol and HDL cholesterol were unrelated ( $r = 0.01$ ).

Men with higher serum total cholesterol concentrations tended to have lower education and reported greater consumption of saturated fat, whereas those with higher HDL cholesterol levels were leaner, physically more active, and consumed more alcohol, compared with men in the lowest cholesterol quintile (Table 1). Age, cigarettes per day, and years of smoking did not differ substantially by total or HDL cholesterol quintile.

During 18.0 years of follow-up (median 14.9 years), 7,545 incident cancer cases were identified. Higher serum total cholesterol was associated with decreased overall cancer incidence in the multivariate model (i.e., comparing highest to lowest quintiles, RR, 0.85; 95% CI, 0.79–0.91;  $P$  trend <0.0001; Table 2). The nonparametric regression

**Table 1. Baseline characteristics of participants according to serum total cholesterol and HDL cholesterol, ATBC Study cohort, 1985 to 2003 (N = 29,093)**

Characteristics	Total cholesterol (mg/dL)			HDL cholesterol (mg/dL)		
	Quintile 1 (<203.9)	Quintile 3 (227.7-249.2)	Quintile 5 (>276.7)	Quintile 1 (<36.2)	Quintile 3 (41.7-47.2)	Quintile 5 (>55.3)
Serum lipids, mg/dL						
Total cholesterol (baseline)	182.9	238.3	306.9	238.1	242.5	240.6
Total cholesterol (at 3-y follow-up)	190.5	232.1	278.0	229.8	234.7	235.2
Total cholesterol change in first 3 y	7.3	-6.2	-28.7	-8.3	-8.5	-7.6
HDL cholesterol (baseline)	45.8	46.3	46.4	31.9	44.3	65.4
HDL cholesterol (at 3-y follow-up)	44.8	44.9	44.6	33.4	43.8	59.2
HDL cholesterol change in first 3 y	-0.5	-1.3	-1.8	+1.5	-0.6	-5.8
Age, y	57.5	57.1	57.0	57.2	57.3	57.2
Smoking history						
Cigarettes/d	20.6	20.2	20.4	20.5	20.2	20.8
Years of smoking	36.1	35.8	35.9	36.1	35.9	35.9
Education, %						
Elementary school or less	77.1	79.2	80.6	77.6	79.8	80.4
Up to junior high school	14.8	13.4	12.5	15.0	13.0	12.2
High school or more	8.1	7.4	6.9	7.3	7.2	7.4
Blood pressure, mm Hg						
Diastolic	86.8	87.9	88.3	87.8	87.3	88.0
Systolic	141.1	142.3	142.7	141.8	141.5	143.1
BMI, kg/m <sup>2</sup>	26.1	26.3	26.5	28.0	26.4	24.4
Leisure-time physical activity, %						
Sedentary	43.7	41.7	41.0	46.1	40.4	42.2
Moderate	49.6	52.2	53.8	49.3	53.0	51.8
Heavy	6.7	6.1	5.2	4.6	6.5	6.0
Height, cm	173.8	173.6	173.2	174.1	173.6	172.8
Alcohol consumption, g/d	17.0	17.0	16.3	11.8	15.9	23.7
Energy intake, kcal/d	2,810	2,822	2,804	2,776	2,831	2,813
Dietary saturate fat intake, g/1,000 kcal/d	17.8	18.4	19.0	17.9	18.6	18.6

NOTE: Data are means or proportions.

plot showed a pattern similar to the categorical analyses, with the multivariate RR decreasing linearly with increasing total cholesterol (Fig. 1A). To minimize the impact of preclinical malignancy on serum cholesterol concentrations in our study, we conducted a lag analysis that excluded cases diagnosed within the first 9 years of follow-up, which showed the inverse association substantially attenuated and no longer statistically significant (RR, 0.96; 95% CI, 0.87-1.06). Progressive attenuation was observed with the exclusion of the first 3, 9, 12, and 15 years of follow-up (Table 2).

The inverse relation of serum total cholesterol was particularly evident and significant for cancers of the lung and liver [highest versus lowest quintile, RR, 0.81 (95% CI, 0.72-0.92; *P* for trend = 0.0006) and 0.66 (95% CI, 0.43-1.01; *P* for trend = 0.007), respectively; Table 2; Fig. 2A]. As in the analysis of all cancers combined, however, these associations were no longer significant when we excluded cases ascertained during the first 9 years of follow-up [lung cancer RR (95% CI), 0.93 (0.78-1.11), 1,327 cases; liver cancer RR (95% CI), 0.89 (0.47-1.67), 92 cases]. Higher serum cholesterol was also associated with decreased risks of the prostate, colorectal, and kidney cancers (albeit with marginal statistical significance), and were also attenuated in the 9-year lag analysis (highest versus lowest quintile, RR, 0.95, 1.18, and 1.04, for the three sites, respectively). Total cholesterol concentrations were unrelated to risk of the other cancer sites examined, and the findings remained essentially unchanged when we used total cholesterol measured in the 3rd year of follow-up or used an average of the two cholesterol determinations (data not shown).

We examined whether the serum total cholesterol-cancer associations were modified by other factors and found that the associations were largely similar across various subgroups of men defined by age (<60 and 60+ years), BMI (<25, 25-29.9, and 30+ kg/m<sup>2</sup>), total fat and alcohol intake (tertiles), years of smoking (tertiles), cigarettes smoked daily (tertiles), and the  $\alpha$ -tocopherol and  $\beta$ -carotene trial supplementation groups (all *P* for interaction  $\geq$ 0.1; data not shown).

Higher serum HDL cholesterol was modestly, but significantly, associated with decreased cancer incidence overall in multivariate models (Table 3; comparing highest to lowest quintile, RR, 0.89; 95% CI, 0.83-0.97; *P* trend = 0.01). The nonparametric regression curve (Fig. 1B) showed a pattern similar to that of the categorical analyses, with the multivariate RR decreasing with increasing serum HDL cholesterol up to ~55 mg/dL. The inverse association remained significant after exclusion of cases diagnosed during the first 12 years of follow-up [RR (95% CI), 0.85 (0.75-0.98), *P* trend = 0.01; *n* = 2,365 cases] and was similar but not statistically significant after excluding the first 15 years of observation [RR (95% CI), 0.85 (0.69-1.02) *P* trend = 0.10; *n* = 1,002 cases].

The weak inverse relation of HDL cholesterol was largely attributed to cancers of the lung, prostate, liver, and hematopoietic system: RR (95% CI) for highest versus lowest quintiles for these sites, respectively, were 0.89 (0.78-1.01), *P* trend = 0.19; 0.89 (0.75-1.06), *P* trend = 0.12; 0.61 (0.38-0.97), *P* trend = 0.05; and 0.71 (0.49-1.04, *P* trend = 0.03. When we excluded cases diagnosed in the first 9 years of follow-up, however, only the inverse associations with lung and liver cancer remained suggestive [RR (95% CI),

0.84 (0.69-1.01) and 0.74 (0.39-1.44), respectively]. Exclusion of cases ascertained during the first 12 years of follow-up also did not eliminate these associations, although the number of cases were small [RR for lung cancer, 0.86 (0.68-1.09) and RR for liver cancer, 0.49 (0.20-1.23)]. In contrast, the inverse associations with prostate and hematopoietic

cancers was not apparent after excluding cases from the first 9 years [RR (95% CI), 0.94 (0.75-1.16) and 1.76 (0.65-2.14), respectively]. Results remained essentially unchanged when we used HDL cholesterol measured in the 3rd year of follow-up or used the average of the two HDL cholesterol values (data not shown).

**Table 2. RRs and 95% CIs of cancer in relation to serum total cholesterol, ATBC Study cohort, 1985 to 2003 (N = 29,093)**

Type of cancer	Total cholesterol (mg/dL)					P
	Quintile 1 (<203.9)	Quintile 2 (203.9-227.6)	Quintile 3 (227.7-249.2)	Quintile 4 (249.3-276.6)	Quintile 5 (>276.7)	
All cancers						
No. of cases	1,616	1,521	1,479	1,503	1,412	
Age-standardized rate*	2,208	2,046	1,956	1,966	1,892	
RR (95% CI) <sup>†</sup>	1 (reference)	0.93 (0.87-1.00)	0.89 (0.83-0.95)	0.89 (0.83-0.96)	0.86 (0.80-0.92)	<0.0001
RR (95% CI) <sup>‡</sup>	1 (reference)	0.92 (0.86-0.99)	0.88 (0.82-0.95)	0.89 (0.83-0.95)	0.85 (0.79-0.91)	<0.0001
Lag analysis						
No. of cases <sup>§</sup>	1,381	1,340	1,313	1,309	1,281	
RR (95% CI) <sup>†,§</sup>	1 (reference)	0.94 (0.88-1.02)	0.93 (0.86-1.00)	0.91 (0.85-0.99)	0.90 (0.83-0.97)	0.006
No. of cases <sup>  </sup>	708	724	708	741	693	
RR (95% CI) <sup>†,  </sup>	1 (reference)	1.01 (0.92-1.12)	0.99 (0.89-1.09)	0.99 (0.90-1.09)	0.96 (0.87-1.06)	0.37
No. of cases <sup>¶</sup>	519	514	506	522	504	
RR (95% CI) <sup>†,¶</sup>	1 (reference)	0.98 (0.87-1.11)	0.97 (0.86-1.09)	0.97 (0.86-1.10)	0.96 (0.85-1.08)	0.49
No. of cases <sup>**</sup>	202	185	206	209	200	
RR (95% CI) <sup>†,**,§</sup>	1 (reference)	0.93 (0.76-1.13)	1.04 (0.86-1.26)	1.01 (0.83-1.23)	1.00 (0.82-1.22)	0.78
Lung cancer						
No. of cases	566	547	498	534	473	
RR (95% CI)	1 (reference)	0.95 (0.84-1.07)	0.87 (0.77-0.98)	0.92 (0.82-1.03)	0.81 (0.72-0.92)	0.0006
Prostate cancer						
No. of cases	323	314	317	330	302	
RR (95% CI)	1 (reference)	0.94 (0.80-1.10)	0.94 (0.81-1.10)	0.97 (0.83-1.13)	0.90 (0.77-1.05)	0.09
Bladder cancer						
No. of cases	113	82	86	100	100	
RR (95% CI)	1 (reference)	0.71 (0.53-0.94)	0.75 (0.57-0.99)	0.86 (0.66-1.13)	0.87 (0.66-1.14)	0.40
Colorectal cancer						
No. of cases	106	116	100	92	93	
RR (95% CI)	1 (reference)	1.05 (0.81-1.37)	0.91 (0.69-1.19)	0.84 (0.63-1.11)	0.86 (0.65-1.13)	0.06
Stomach cancer						
No. of cases	73	65	79	52	65	
RR (95% CI)	1 (reference)	0.87 (0.62-1.21)	1.05 (0.76-1.45)	0.69 (0.48-0.99)	0.86 (0.62-1.21)	0.48
Kidney cancer						
No. of cases	60	68	58	54	50	
RR (95% CI)	1 (reference)	1.08 (0.76-1.52)	0.91 (0.63-1.30)	0.83 (0.57-1.20)	0.76 (0.52-1.10)	0.08
Pancreatic cancer						
No. of cases	59	53	55	47	59	
RR (95% CI)	1 (reference)	0.87 (0.60-1.26)	0.90 (0.63-1.31)	0.77 (0.52-1.13)	0.96 (0.67-1.38)	0.73
Hematopoietic						
No. of cases	67	79	54	61	63	
RR (95% CI)	1 (reference)	1.15 (0.83-1.60)	0.79 (0.55-1.12)	0.89 (0.63-1.26)	0.92 (0.65-1.30)	0.22
Oropharynx cancer						
No. of cases	42	32	28	38	42	
RR (95% CI)	1 (reference)	0.75 (0.48-1.20)	0.65 (0.40-1.05)	0.89 (0.58-1.39)	1.00 (0.65-1.54)	0.56
Larynx cancer						
No. of cases	23	29	33	36	21	
RR (95% CI)	1 (reference)	1.24 (0.71-2.14)	1.42 (0.83-2.41)	1.57 (0.93-2.65)	0.90 (0.50-1.64)	0.77
Liver cancer						
No. of cases	55	38	34	30	34	
RR (95% CI)	1 (reference)	0.69 (0.46-1.05)	0.63 (0.41-0.97)	0.56 (0.36-0.88)	0.66 (0.43-1.01)	0.007
Brain cancer						
No. of cases	5	12	14	15	10	
RR (95% CI)	1 (reference)	2.31 (0.81-6.57)	2.78 (1.00-7.72)	2.99 (1.08-8.24)	1.98 (0.67-5.81)	0.23
Melanoma						
No. of cases	17	14	19	12	21	
RR (95% CI)	1 (reference)	0.80 (0.40-1.64)	1.11 (0.58-2.15)	0.72 (0.34-1.50)	1.24 (0.65-2.36)	0.44
Esophageal cancer						
No. of cases	17	20	25	12	23	
RR (95% CI)	1 (reference)	1.15 (0.60-2.20)	1.44 (0.77-2.67)	0.69 (0.33-1.45)	1.37 (0.73-2.57)	0.65

\*Rates are per 100,000 person-years, directly standardized to the age distribution of the cohort.

<sup>†</sup>Adjusted for age.

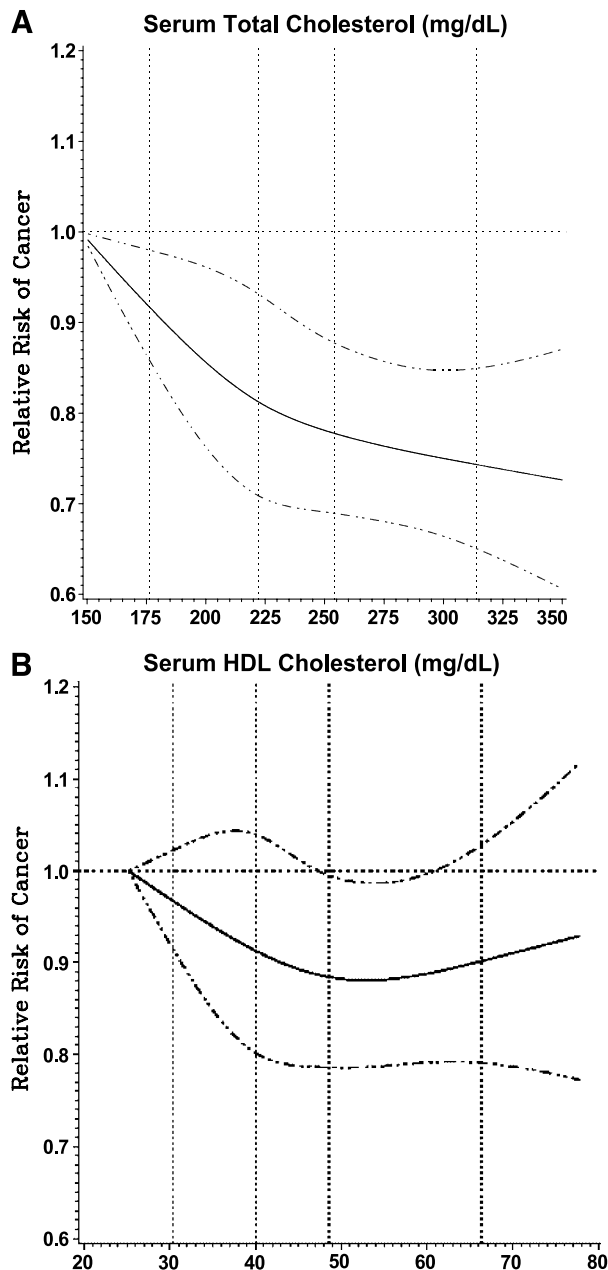
<sup>‡</sup>Adjusted for age, intervention, level of education, systolic blood pressure, BMI, physical activity, duration of smoking, number of cigarettes smoked per day, saturates fat intake, polyunsaturated fat intake, total calorie, alcohol consumption, and serum HDL cholesterol.

<sup>§</sup>Excluded cases ascertained during the first 3 y of follow-up.

<sup>||</sup>Excluded cases ascertained during the first 9 y of follow-up.

<sup>¶</sup>Excluded cases ascertained during the first 12 y of follow-up.

<sup>\*\*</sup>Excluded cases ascertained during the first 15 y of follow-up.



**Figure 1.** Nonparametric regression curve for the association between total cholesterol/HDL cholesterol and cancer risk. The lines are natural cubic splines showing the shape of the dose-response curve for cancer risk according to total cholesterol (**A**) or HDL cholesterol (**B**) on a continuous basis. The graphic display is truncated at 1% and 99% on the basis of the distribution of total cholesterol or HDL cholesterol. The model is adjusted for age, intervention, level of education, systolic blood pressure, BMI, physical activity, duration of smoking, number of cigarettes smoked per day, saturated fat intake, total calorie, alcohol consumption, serum total cholesterol, and serum HDL cholesterol.

In exploratory analyses, associations between HDL cholesterol and cancer were largely similar across other subgroups of men defined by age (<60 and 60+ years), BMI (<25, 25-29.9, and 30+ kg/m<sup>2</sup>), total fat and alcohol intake

(tertiles), years of smoking (tertiles), cigarettes smoked daily (tertiles), and the  $\alpha$ -tocopherol and  $\beta$ -carotene trial supplementation groups (all  $P$  for interaction  $\geq 0.05$ ; data not shown).

## Discussion

We observed that men with higher serum total cholesterol concentrations experienced lower cancer incidence rates compared with men with lower levels. This overall association was greatly attenuated, however, when we excluded cases diagnosed during the first half of our 18-year follow-up period, indicating that lower serum cholesterol may be a marker of existing malignancy and not a causal factor. Greater serum HDL cholesterol was modestly, but significantly, associated with decreased overall cancer risk, especially for cancers of the lung, liver, and the hematopoietic system. These associations for lung and liver cancers were stable during follow-up.

Several studies have found modestly higher cancer mortality (1-11) and incidence (10, 12-14) among persons with low serum total cholesterol, and our findings based on more than 7,500 incident cases and nearly 20 years of follow-up are consistent with these observations. Whether this association has any causal basis has remained controversial, however. The Multiple Risk Factor Intervention Trial and the Lipid Research Clinics Coronary Primary Prevention Trial observed that total cholesterol concentrations decreased ~5 years before cancer death (11) and 2 years before cancer diagnosis (17), respectively, indicating the possibility of preclinical effects of malignancies on serum levels; for example, through effects on cholesterol absorption, transport, metabolism, or utilization. Although the timing of cholesterol depression with respect to specific cancer sites, including of the lung and liver, has not been delineated, our observation of essentially null associations with total cholesterol after exclusion of cases diagnosed during the first 9 years of follow-up, along with larger declines in cholesterol concentrations from baseline to 3 years for cases diagnosed within 9 years of blood collection, supports the idea that subclinical and undiagnosed malignancy played a role in the prior studies' findings. It is also possible that cholesterol acts as a component of acute phase response that indicates or causes a wide variety of future diseases, including cancer, as previously suggested (30).

Our study is unique among prior similar investigations in having serum HDL cholesterol measurements for the entire cohort of 29,000 men. Higher HDL concentrations were related to modestly decreased risk of cancer overall, and this association remained after excluding cases diagnosed during the first 15 years of follow-up, arguing against an effect of preclinical disease on serum concentrations. Our findings are consistent with the Framingham Offspring Study, which observed an inverse (albeit, not statistically significant) association between HDL cholesterol and cancer risk; however, this evaluation was based on very few (200) cases (31). Biological mechanisms that might account for a HDL cholesterol-cancer relationship are not well understood, although HDL regulation of cell cycle entry through a mitogen-activated protein kinase-dependent pathway (18) and apoptosis (19), modulation of cytokine production, and anti-oxidative function (32) have been considered and are biologically plausible.

We found an inverse association between serum HDL cholesterol and risk of lung cancer that was also stable to exclusion of cases diagnosed early during follow-up. Three case-control studies observed lower serum HDL cholesterol in lung cancer patients compared with controls (33-35), as did the prospective Atherosclerosis Risk in

Communities study (23). In the latter study, the inverse relationship was more pronounced among former, and not current, smokers. Although the ATBC Study participants were smokers at study entry, we observed no interaction between smoking dose or duration, HDL cholesterol, and lung cancer. The Atherosclerosis Risk in Communities

**Table 3. RRs and 95% CIs of cancer in relation to serum HDL cholesterol, ATBC Study cohort, 1985 to 2003 (N = 29,093)**

Type of cancer	HDL cholesterol (mg/dL)					P
	Quintile 1 (<36.2)	Quintile 2 (36.2-41.6)	Quintile 3 (41.7-47.2)	Quintile 4 (47.3-55.2)	Quintile 5 (>55.3)	
All cancers						
No. of cases	1,515	1,476	1,537	1,519	1,498	
Age-standardized rate*	2,108	1,959	2,006	1,960	2,029	
RR (95% CI) <sup>†</sup>	1 (reference)	0.93 (0.86-1.00)	0.95 (0.89-1.02)	0.93 (0.87-1.00)	0.96 (0.90-1.03)	0.48
RR (95% CI) <sup>‡</sup>	1 (reference)	0.92 (0.85-0.98)	0.93 (0.86-0.99)	0.90 (0.83-0.97)	0.89 (0.83-0.97)	0.01
Lag analysis						
No. of cases <sup>§</sup>	1,308	1,298	1,355	1,346	1,317	
RR (95% CI) <sup>†,§</sup>	1 (reference)	0.93 (0.86-1.00)	0.94 (0.87-1.02)	0.91 (0.84-0.99)	0.90 (0.83-0.98)	0.03
No. of cases <sup>  </sup>	689	709	737	739	712	
RR (95% CI) <sup>†,  </sup>	1 (reference)	0.93 (0.84-1.03)	0.94 (0.85-1.03)	0.92 (0.83-1.01)	0.86 (0.77-0.96)	0.008
No. of cases <sup>¶</sup>	491	514	544	513	503	
RR (95% CI) <sup>†,¶</sup>	1 (reference)	0.95 (0.84-1.08)	0.95 (0.84-1.08)	0.88 (0.77-0.99)	0.85 (0.75-0.98)	0.01
No. of cases <sup>**</sup>	198	197	194	196	217	
RR (95% CI) <sup>†,**,¶</sup>	1 (reference)	0.88 (0.73-1.08)	0.81 (0.66-0.99)	0.79 (0.64-0.97)	0.85 (0.69-1.02)	0.10
Lung cancer						
No. of cases	495	499	514	564	546	
RR (95% CI)	1 (reference)	0.92 (0.81-1.05)	0.91 (0.80-1.03)	0.96 (0.85-1.09)	0.89 (0.78-1.01)	0.19
Prostate cancer						
No. of cases	310	327	345	321	283	
RR (95% CI)	1 (reference)	0.99 (0.85-1.16)	1.03 (0.88-1.20)	0.95 (0.81-1.11)	0.89 (0.75-1.06)	0.12
Bladder cancer						
No. of cases	102	105	98	83	93	
RR (95% CI)	1 (reference)	0.98 (0.75-1.30)	0.91 (0.69-1.21)	0.77 (0.57-1.04)	0.90 (0.66-1.22)	0.28
Colorectal cancer						
No. of cases	106	110	83	97	111	
RR (95% CI)	1 (reference)	0.99 (0.76-1.30)	0.73 (0.55-0.98)	0.85 (0.64-1.14)	1.01 (0.76-1.35)	0.99
Stomach cancer						
No. of cases	66	57	78	76	57	
RR (95% CI)	1 (reference)	0.85 (0.60-1.22)	1.17 (0.84-1.63)	1.15 (0.82-1.62)	0.90 (0.61-1.32)	0.95
Kidney cancer						
No. of cases	63	75	52	60	40	
RR (95% CI)	1 (reference)	1.21 (0.87-1.70)	0.87 (0.60-1.27)	1.05 (0.73-1.52)	0.80 (0.52-1.22)	0.20
Pancreatic cancer						
No. of cases	59	41	68	44	61	
RR (95% CI)	1 (reference)	0.65 (0.43-0.97)	1.06 (0.74-1.52)	0.67 (0.45-1.00)	0.94 (0.64-1.40)	0.97
Hematopoietic						
No. of cases	77	74	67	54	52	
RR (95% CI)	1 (reference)	0.95 (0.69-1.30)	0.85 (0.61-1.18)	0.68 (0.47-0.97)	0.71 (0.49-1.04)	0.03
Oropharynx cancer						
No. of cases	28	36	28	41	49	
RR (95% CI)	1 (reference)	1.10 (0.67-1.81)	0.78 (0.46-1.33)	1.03 (0.62-1.69)	1.06 (0.64-1.76)	0.76
Larynx cancer						
No. of cases	27	25	29	22	39	
RR (95% CI)	1 (reference)	0.86 (0.50-1.49)	0.95 (0.56-1.63)	0.70 (0.39-1.25)	1.20 (0.70-2.05)	0.47
Liver cancer						
No. of cases	55	34	32	34	36	
RR (95% CI)	1 (reference)	0.60 (0.39-0.93)	0.55 (0.35-0.86)	0.58 (0.37-0.91)	0.61 (0.38-0.97)	0.05
Brain cancer						
No. of cases	9	9	13	10	15	
RR (95% CI)	1 (reference)	0.87 (0.34-2.20)	1.16 (0.49-2.75)	0.83 (0.33-2.11)	1.11 (0.45-2.73)	0.80
Melanoma						
No. of cases	18	18	23	13	11	
RR (95% CI)	1 (reference)	1.06 (0.55-2.05)	1.44 (0.77-2.70)	0.85 (0.41-1.78)	0.87 (0.39-1.94)	0.59
Esophageal cancer						
No. of cases	13	17	13	18	36	
RR (95% CI)	1 (reference)	1.10 (0.53-2.28)	0.75 (0.35-1.65)	0.93 (0.45-1.96)	1.60 (0.80-3.19)	0.08

\*Rates are per 100,000 person-years, directly standardized to the age distribution of the cohort.

<sup>†</sup>Adjusted for age.

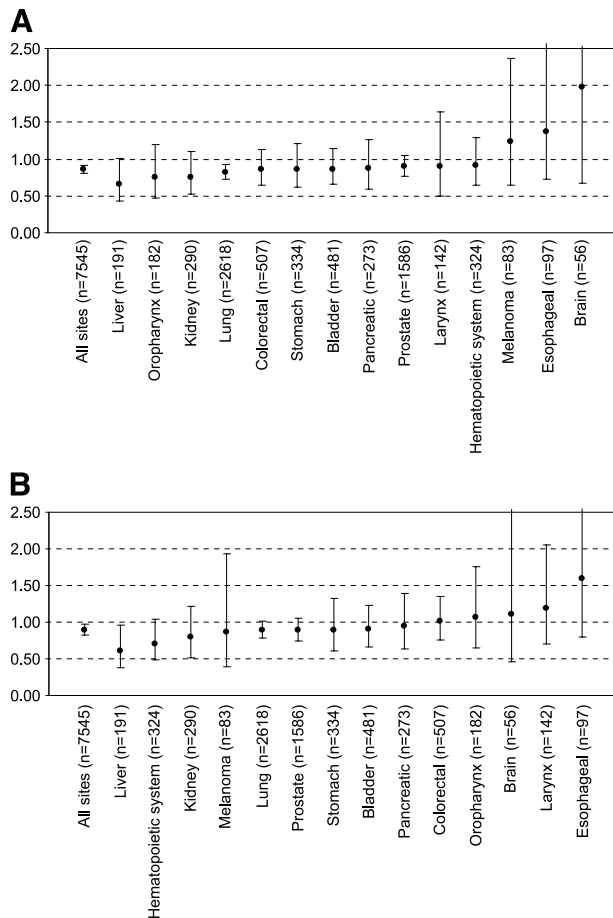
<sup>‡</sup>Adjusted for age, intervention, level of education, systolic blood pressure, BMI, physical activity, duration of smoking, number of cigarettes smoked per day, saturated fat intake, polyunsaturated fat intake, total calorie intake, alcohol consumption, and serum total cholesterol.

<sup>§</sup>Excluded cases ascertained during the first 3 y of follow-up.

<sup>||</sup>Excluded cases ascertained during the first 9 y of follow-up.

<sup>¶</sup>Excluded cases ascertained during the first 12 y of follow-up.

<sup>\*\*</sup>Excluded cases ascertained during the first 15 y of follow-up.



**Figure 2.** RRs and 95% CIs for the 5th versus 1st quintile of total cholesterol (A) and HDL cholesterol (B) and cancer risk.

study showed an inverse HDL–lung cancer association even after exclusion of cases diagnosed within 5 years of baseline (23), and although data are lacking from other studies, taken together with the present findings, an etiologic role for low HDL cholesterol in lung cancer cannot be excluded.

The findings for serum HDL cholesterol and risk of liver cancer were somewhat unexpected. Because most lipoproteins are synthesized in the liver, the plasma lipid (and lipoprotein) patterns could result from subclinical liver carcinogenesis (36, 37). Our findings of an inverse association after excluding cases diagnosed during the first 12 years of follow-up may indicate some etiologic role for HDL in liver carcinogenesis, although exclusion of a longer lag period in other prospective studies with sufficient cases may be necessary to confirm our data.

The major strengths of our investigation include the use of prediagnostic serum, a large study sample with serum cholesterol prospectively measured, and detailed information on dietary and lifestyle factors, including direct measurements of blood pressure and anthropometry that minimized bias from self-reports. With 18 years of observation, we were able to examine the risk associations after excluding successive years of the cancers diagnosed earlier during follow-up to evaluate and minimize reverse causa-

tion. In contrast to most previous studies, we measured both total and HDL cholesterol concentrations and observed high correlations between their determinations 3 years apart ( $r = 0.74$  and  $0.77$ , respectively), supporting internal consistency and validity. Total and HDL cholesterol concentrations were also comparable with those in the U.S. population (smokers and nonsmokers): low total cholesterol ( $<230$  mg/dL) and HDL cholesterol ( $<40$  mg/dL) were observed in 45% and 35% for our study compared with 50% and 33% among men in the United States (38).

Our investigation included only male cigarette smokers and our findings may not be directly generalizable to women and nonsmokers. The cholesterol–cancer associations we observed did not differ according to smoking dose or duration, however, and they were not confounded by smoking levels. Another limitation of the study is that we did not have information regarding use of cholesterol-lowering medications or other lipid fractions such as LDL cholesterol and triglycerides; however, with the average total-to-HDL cholesterol ratio being 5.36 in our study, the total cholesterol findings are likely to have been driven largely by LDL cholesterol and triglycerides. It is theoretically possible that our findings were influenced by competing risks; that is, if men with higher total serum cholesterol are more likely to die from cardiovascular causes, they might be at reduced risk of developing (or being diagnosed with) cancer. Because information on cholesterol levels and other cardiovascular risk factors was not updated during the longer follow-up period, we were not able to fully evaluate these characteristics as time-dependent variables.

In summary, higher circulating total and HDL cholesterol concentrations were associated with decreased risk of cancer, particularly for cancers of the lung and liver (total cholesterol) and lung, liver, and hematopoietic malignancies (HDL cholesterol). An influence of preclinical disease to lower cholesterol concentrations seems to explain some of the associations observed, particularly for total cholesterol, but we cannot completely rule out an etiologic role for low serum (primarily HDL) cholesterol. Additional studies in other populations that include women and nonsmokers, as well as experimental investigations of potential mechanisms such as cell membrane and inflammation effects, and more detailed analyses of differences by cancer stage or aggressiveness, will be useful for a more complete understanding of the circulating cholesterol–cancer relationship.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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