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Pre-diagnostic Total and High Density Lipoprotein Cholesterol and Risk of Cancer

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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 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.

Results—Higher serum total cholesterol concentration was associated with decreased risk of cancer overall (RR for comparing high versus low quintile=0.85, 95%CI=0.79–0.91; P trend < 0.001; >276.7 versus <203.9 mg/dL), and the inverse association was particularly evident for cancers of the lung and liver. These associations were no longer significant, however, when cases diagnosed during the first nine 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%CI=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.

Keywords

serum; cholesterol; high density lipoprotein cholesterol; cancer; risk; prospective; cohort

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) (15). One prospective study showed that the cholesterol-cancer association was present for serum determinations made six or more years before the diagnosis of cancer (16). In 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 about 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 4–6 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 whether α -tocopherol or β -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 aged 50–69 years in southwestern Finland who smoked at least five cigarettes per day were randomized to receive supplements (50 mg/day of α -tocopheryl acetate, 20 mg/day of β -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 β -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 prior to the study's 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 approximately 100% cancer diagnosis coverage for nationwide (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 cytological 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, kg/m²) 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°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 cholesterol with dextran sulfate and magnesium chloride. Baseline serum cholesterol levels were successfully analyzed in 29,093 men (99.9%). At the third-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 hazards regression analysis to generate relative risks (RRs) and 95% confidence intervals (CIs) 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 (α -tocopheryl acetate and β -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 1000 kcal intake of total energy), polyunsaturated fat intake (per 1000 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 non-parametric 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 performed 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., Cary, North Carolina). All statistical tests were two-sided.

RESULTS

Average total and HDL cholesterol values for the study population at baseline were 241.2 mg/dl (standard deviation (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 concentration 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 quintiles (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 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 pre-clinical malignancy on serum cholesterol concentrations in our study, we conducted a lag analysis that excluded cases diagnosed within the first nine 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 three, nine, twelve and fifteen 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 and 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 nine 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 nine 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 third 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^2), total fat and alcohol intake (tertiles), years of smoking (tertiles), cigarettes smoked daily (tertiles), and the α -tocopherol and β -carotene trial supplementation groups (all p for interaction 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 approximately 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 significantly 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 (95% CI=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 nine years (RR's (95% CI) of 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 third year of follow-up or used the average of the two HDL cholesterol values (data not shown).

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/m²), total fat and alcohol intake (tertiles), years of smoking (tertiles), cigarettes smoked daily (tertiles), and the α -tocopherol and β -carotene trial supplementation groups (all p for interaction = 0.05; data not shown).

DISCUSSION

We observed that men with higher serum total cholesterol concentrations experienced lower cancer incidence rates compared to 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 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 over 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 (MRFIT) and the Lipid Research Clinics Coronary Primary Prevention Trial observed that total cholesterol concentrations decreased about 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 nine years of follow-up, along with larger declines in cholesterol concentrations from baseline to three years for cases diagnosed within nine years of blood collection, supports the idea that sub-clinical 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 an 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 (ARIC) 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 ARIC 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 etiological 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 etiological 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.

Major strengths of our investigation include the use of pre-diagnostic 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 causation. In contrast to most previous studies, we measured both total and HDL cholesterol concentrations, and observed high correlations between their determinations three years apart ($r=0.74$ and 0.77 , respectively), supporting internal consistency and validity. Total and HDL cholesterol concentrations were also comparable to those in the U.S. population (smokers and nonsmokers): low total ($<230\text{mg/dl}$) and HDL cholesterol ($<40\text{ mg/dL}$) were observed in 45% and 35% for our study as compared with 50 and 33% among men in the U.S. (38).

Our investigation included only male cigarette smokers and our findings may not be directly generalizable to women and non-smokers. 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 lipids fractions such as low density lipoprotein (LDL) cholesterol and triglycerides; however, with the average total: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 pre-clinical disease to lower cholesterol concentrations appears 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.

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Abbreviations

HDL	high density lipoprotein
RR	relative risk
CI	confidence interval
BMI	body mass index
SD	standard deviation

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a. Serum Total Cholesterol (mg/dl)

b. Serum HDL Cholesterol (mg/dl)

Figure 1. Nonparametric Regression Curve for the Association between Total Cholesterol and 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 or HDL cholesterol on a continuous scale. The graphic display is truncated at 1 percent and 99 percent on the basis of the distribution of total cholesterol or HDL cholesterol. The model is adjusted for age, trial intervention group, education, systolic blood pressure, body mass index, physical activity, duration of smoking, daily cigarettes smoked, total energy and saturated fat intake, alcohol consumption, and serum total cholesterol and serum HDL cholesterol.

Figure 2. HRs and 95% CI for the 5th versus 1st quintile of Total Cholesterol (figure 2-a) and HDL Cholesterol (figure 2-b) and Cancer Risk

Baseline characteristics of participants, according to serum total cholesterol and HDL cholesterol, ATBC Cancer Prevention Study Cohort, 1985–2003 (N=29,093)^a

TABLE 1

Characteristics	Total cholesterol					HDL cholesterol				
	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-year follow-up)	190.5	232.1	278.0	229.8	234.7	235.2				
Total cholesterol change in first 3 years	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-year follow-up)	44.8	44.9	44.6	33.4	43.8	59.2				
HDL cholesterol change in first 3 years	–0.5	–1.3	–1.8	+1.5	–0.6	–5.8				
Age, years	57.5	57.1	57.0	57.2	57.3	57.2				
Smoking history										
Cigarettes, numbers/day	20.6	20.2	20.4	20.5	20.2	20.8				
Years smoked, years	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, mmHg										
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 ²	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/day	17.0	17.0	16.3	11.8	15.9	23.7				
Energy intake, kcal/day	2810	2822	2804	2776	2831	2813				

Characteristics	Total cholesterol			HDL cholesterol		
	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)
Dietary saturated fat intake, g/1,000 kcal/day	17.8	18.4	19.0	17.9	18.6	18.6

^aMeans or proportions.

TABLE 2

Relative risks (RR) and 95% confidence intervals (CI) of cancer in relation to serum total cholesterol, 1985–2003 (N=29,093)

Type of Cancer	Total cholesterol (mg/dl)					P trend
	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 ^a	2208	2046	1956	1966	1892	
RR (95% CI) ^b	1 (ref)	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) ^c	1 (ref)	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 ^d	1,381	1,340	1,313	1,309	1,281	
RR (95% CI) ^{c, d}	1 (ref)	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 ^e	708	724	708	741	693	
RR (95% CI) ^{c, e}	1 (ref)	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 ^f	519	514	506	522	504	
RR (95% CI) ^{c, f}	1 (ref)	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 ^g	202	185	206	209	200	
RR (95% CI) ^{c, g}	1 (ref)	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 (ref)	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 (ref)	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 (ref)	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	

Type of Cancer	Total cholesterol (mg/dl)					P trend
	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)	
RR (95% CI)	1 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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	

Type of Cancer	Total cholesterol (mg/dl)					P trend
	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)	
RR (95% CI)	1 (ref)	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

^aRates are per 100,000 person-years, directly standardized to the age distribution of the cohort.

^bAdjusted for age.

^cAdjusted for age, intervention, level of education, systolic blood pressure, body mass index, 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.

^dExcluded cases ascertained during the first 3 years of follow-up.

^eExcluded cases ascertained during the first 9 years of follow-up.

^fExcluded cases ascertained during the first 12 years of follow-up.

^gExcluded cases ascertained during the first 15 years of follow-up.

TABLE 3

Relative risks (RR) and 95% confidence intervals (CI) of cancer in relation to serum HDL cholesterol, 1985–2003 (N=29,093)

Type of Cancer	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)	P trend
All cancers						
No. of cases	1,515	1,476	1,537	1,519	1,498	
Age-standardized rate ^a	2108	1959	2006	1960	2029	
RR (95% CI) ^b	1 (ref)	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) ^c	1 (ref)	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 ^d	1,308	1,298	1,355	1,346	1,317	
RR (95% CI) ^{c, d}	1 (ref)	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 ^e	689	709	737	739	712	
RR (95% CI) ^{c, e}	1 (ref)	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 ^f	491	514	544	513	503	
RR (95% CI) ^{c, f}	1 (ref)	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 ^g	198	197	194	196	217	
RR (95% CI) ^{c, g}	1 (ref)	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 (ref)	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 (ref)	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 (ref)	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	

Type of Cancer	HDL cholesterol (mg/dl)					P trend
	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)	
RR (95% CI)	1 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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 (ref)	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	

Type of Cancer	HDL cholesterol (mg/dl)					P trend
	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)	
RR (95% CI)	1 (ref)	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

^aRates are per 100,000 person-years, directly standardized to the age distribution of the cohort.

^bAdjusted for age.

^cAdjusted for age, intervention, level of education, systolic blood pressure, body mass index, physical activity, duration of smoking, number of cigarettes smoked per day, saturates fat intake, polyunsaturated fat intake, total calorie intake, alcohol consumption, and serum total cholesterol.

^dExcluded cases ascertained during the first 3 years of follow-up.

^eExcluded cases ascertained during the first 9 years of follow-up.

^fExcluded cases ascertained during the first 12 years of follow-up.

^gExcluded cases ascertained during the first 15 years of follow-up.