

Association of low plasma cholesterol with mortality for cancer at various sites in men: 17-y follow-up of the prospective Basel study¹⁻³

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ABSTRACT

Background: Low serum cholesterol has been associated with an increased risk of cancer mortality in various studies, which has led to uncertainty regarding the benefit of lower blood cholesterol.

Objective: The aim of our study was to evaluate the association between low blood cholesterol (<5.16 mmol/L) and cancer at sites that have rarely been evaluated. We placed special emphasis on the potential confounding effect of antioxidant vitamins.

Design: Plasma concentrations of cholesterol and antioxidant vitamins were measured in 1971–1973 in 2974 men working in Basel, Switzerland. In 1990, the vital status of all participants was assessed.

Results: Two hundred ninety of the participants had died from cancer, 87 from lung, 30 from prostate, 28 from stomach, and 22 from colon cancer. Group means for plasma cholesterol concentrations did not differ significantly between survivors and those who died from cancer at any of the studied sites. With plasma cholesterol, vitamins C and E, retinol, carotene, smoking, and age accounted for in a Cox model, an increase in total cancer mortality in lung, prostate, and colon but not in stomach cancer mortality was observed in men >60 y of age with low plasma cholesterol. When data from the first 2 y of follow-up were excluded from the analysis, the relative risk estimates remained practically unchanged with regard to lung cancer but decreased for colon, prostate, and overall cancer.

Conclusions: Increased cancer mortality risks associated with low plasma cholesterol were not explained by the confounding effect of antioxidant vitamins, but were attributed in part to the effect of preexisting cancer. *Am J Clin Nutr* 2000;71:569–74.

KEY WORDS Cancer mortality, low plasma cholesterol, cohort study, men, elderly, antioxidants, vitamins, lung cancer, colon cancer, prostate cancer, stomach cancer, Switzerland

INTRODUCTION

Studies of all-cause mortality and serum cholesterol concentration have found a U-shaped association among men, indicating a higher total mortality rate for those with high and those with low concentrations of serum cholesterol (1). Hypercholesterolemia is a major risk factor for coronary heart disease (2). Low serum cholesterol, on the other hand, has

been associated with an increased risk of cancer and other noncoronary heart disease mortality (3, 4). These observations have led to uncertainty regarding strategies to lower blood cholesterol within whole populations (5).

Detailed analysis of cancer epidemiology shows that low cholesterol concentrations were associated with a significantly increased risk of cancer in many (6–16), but not in all, of the observational studies (17–22). Four studies (7, 17, 23, 24) observed a significant association with lung cancer; other surveys showed non-significant results (25, 26). Higher colon cancer risk in individuals with low cholesterol concentrations was observed in some studies (8, 27–29) but not in others (23, 30–32), and a few positive associations were also reported (9, 33). The results of the limited number of studies on stomach (9, 15, 17, 30, 34) and prostate (9, 15, 17, 30) cancer did not overall suggest an association.

Several explanations of the inverse association between low serum cholesterol and cancer have been proposed (3), and there may be a direct causal link between low cholesterol and cancer. It is also possible that the association is secondary to confounding factors such as serum retinol, vitamin E, and β -carotene. Furthermore, competing risks of death, particularly from coronary heart disease, may cause the inverse relation. Low serum cholesterol may also have been caused by undetected cancer.

The 17-y follow-up of the prospective Basel study allowed us to study the association of low plasma cholesterol with mortality from cancer at various sites. Specific cancer sites that have rarely been analyzed by other investigators, such as the stomach and prostate, were studied and the potentially confounding effects of vitamins C and E, retinol, and carotene were controlled for. Furthermore, the cancer mortality risk of older men was compared with that of younger study participants.

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SUBJECTS AND METHODS

Subjects

In 1971–1973, 2974 men were recruited for a cohort study in Basel, Switzerland. Subjects were healthy volunteers who worked in major chemical and pharmaceutical companies in Basel. At recruitment, all participants had a clinical examination, laboratory investigations, and completed a questionnaire. Blood samples were drawn with the subjects in a fasting state. Plasma cholesterol as well as plasma vitamins C and E, retinol, and carotene (80% β -carotene and 20% α -carotene) were measured and other data such as (potential) risk factors, eg, smoking behavior and plasma triacylglycerol concentration, were collected to form the baseline data for the present analysis. With regard to smoking, only smoking status and number of cigarettes smoked daily at entry to the study were assessed; no information was collected on past smoking habits, duration of smoking, age at which smoking started, or depth of inhalation. Light smokers (≤ 5 cigarettes/d) were coded as nonsmokers. In 1990, vital status was assessed for the total cohort of the 2974 men. Information about deaths was provided by employers, relatives, and local authorities. Death certificates were used to identify causes of deaths. A total of 801 men died during the 17 y of follow-up, including 290 from cancer [*International Classification of Diseases, Injuries, and Causes of Death*, 8th revision (ICD-8), codes 140–239 (35)]. The malignancies were grouped into lung cancer ($n = 87$; ICD-8 code 162), prostate cancer ($n = 30$; ICD-8 code 185), stomach cancer ($n = 28$; ICD-8 code 151), colon cancer ($n = 22$; ICD-8 code 153), and “all cancers” ($n = 290$). Because it was impossible to identify persons with undiagnosed cancer at recruitment, the main analysis excluded the individuals who died from cancer within the first 2 y of follow-up ($n = 14$).

METHODS

Laboratory analysis

Details of the laboratory analysis were described elsewhere (36). Briefly, the plasma total cholesterol concentration was measured within 3 d by a method comparable with the cholesterol oxidase *p*-aminophenazone method (37). Retinol, α -tocopherol, and carotene (80% β -carotene and 20% α -carotene) were measured by methods that are fairly comparable with current HPLC procedures. For the analysis of ascorbic acid, the freshly obtained plasma was stabilized with metaphosphoric acid. The vitamins were measured after a few weeks or months of storage at -20°C . All plasma concentrations of fat-soluble vitamins were correlated with plasma cholesterol concentrations (retinol: $r = 0.25$; carotene: $r = 0.23$; and vitamin E: $r = 0.56$), whereas only vitamin E ($r = 0.50$) and retinol ($r = 0.39$) concentrations

were distinctly correlated with plasma triacylglycerol (38). The strongest correlations were found for the sum of cholesterol and triacylglycerol (retinol: $r = 0.41$; vitamin E: $r = 0.64$). Therefore, retinol, carotene, and vitamin E were lipid-adjusted by linear regression to prevent misclassification of the explanatory variables and allow an unbiased interpretation of the explanatory variables. Retinol and vitamin E were adjusted in each participant to the sum of cholesterol (5.7 mmol/L, or 220 mg/dL) and triacylglycerol (2.9 mmol/L, or 110 mg/dL) equal to 8.6 mmol/L (330 mg/dL) and carotene was adjusted for cholesterol equal to 5.7 mmol/L (220 mg/dL). There were no missing data for the variables under consideration (36).

Statistical analysis

The average age and number of smokers as well as group means and SEs of cholesterol and vitamin concentrations are provided for those who died from cancer and survivors. Group means of nutrient concentrations were compared by analysis of covariance with adjustment for smoking habits and age; the least-squares means were compared by *t* tests with Bonferroni α adjustment. Inferential analysis of the explanatory variables was based on the Cox proportional hazards regression model for survival data. We examined the relation between plasma cholesterol concentrations and cancer risk by comparing a “low” category [concentration below the first quartile, ie, <5.16 mmol/L (<199 mg/dL)] with the category of all higher concentrations. For the vitamins considered (except vitamin C: 22.7 $\mu\text{mol/L}$), the first quartile was used as a cutoff, ie, 30.0 $\mu\text{mol/L}$ for vitamin E (adjusted for lipids), 2.45 $\mu\text{mol/L}$ for retinol (adjusted for lipids), and 0.23 $\mu\text{mol/L}$ for carotene (adjusted for cholesterol). According to a stepwise selection process, the above-mentioned explanatory variables together with smoking status entered the regression model on the basis of computed error probabilities. This allowed the identification of a subset of variables that yielded a significant contribution ($\alpha = 5\%$) when added to all other variables in the subset. Besides these variables, all pairwise interactions, including interactions with age, were allowed for selection. The statistical analyses were done by using BMDP statistical software (University of California, Berkeley, CA). Results regarding the vitamins considered were described elsewhere (36) and are not presented here.

RESULTS

Descriptive analysis

The mean baseline characteristics of men who died from cancer ($n = 290$) and survivors ($n = 2173$) are shown in **Tables 1** and **2** (36). Group means for plasma concentrations of cholesterol did not differ significantly between survivors and those who died from

TABLE 1

Mean age and smoking habits at baseline in 1971–1973 for survivor and cancer groups: 17-y follow-up of the Basel study

	Survivors ($n = 2173$)	Lung cancer ($n = 87$)	Prostate cancer ($n = 30$)	Stomach cancer ($n = 28$)	Colon cancer ($n = 22$)	All cancers ($n = 290$)
Age in 1971–1973	49 ± 9.2^1	61 ± 6.4	63.8 ± 6.9	59.1 ± 8.1	60.6 ± 8.1	59.7 ± 7.8
Number of smokers	706 (32.5) ²	62 (71)	12 (40)	11 (39)	7 (32)	136 (47)

¹ $\bar{x} \pm \text{SD}$.

²Percentage in parentheses.

TABLE 2

Baseline plasma cholesterol and vitamin concentrations of survivor and cancer groups: 17-y follow-up of the Basel study¹

	Survivors (n = 2173)	Lung cancer (n = 87)	Prostate cancer (n = 30)	Stomach cancer (n = 28)	Colon cancer (n = 22)	All cancers (n = 290)
Cholesterol (mmol/L)	5.84 ± 0.02	5.85 ± 0.11	5.85 ± 0.19	5.73 ± 0.21	5.69 ± 0.21	5.79 ± 0.06
Carotene (μmol/L) ²	0.44 ± 0.01	0.31 ± 0.02 ³	0.35 ± 0.04	0.31 ± 0.04 ³	0.46 ± 0.07	0.36 ± 0.01 ³
Carotene adjusted to 5.7 mmol C/L (μmol/L) ²	0.43 ± 0.01	0.31 ± 0.02 ³	0.36 ± 0.04	0.30 ± 0.03 ³	0.46 ± 0.07	0.35 ± 0.01 ³
Retinol (μmol/L)	2.87 ± 0.01	2.88 ± 0.08	2.83 ± 0.11	2.69 ± 0.10	2.98 ± 0.16	2.87 ± 0.04
Retinol adjusted to 8.6 mmol C+T/L (μmol/L)	2.81 ± 0.01	2.78 ± 0.06	2.79 ± 0.10	2.65 ± 0.09	2.94 ± 0.14	2.80 ± 0.03
Vitamin E (μmol/L)	36.5 ± 0.2	36.1 ± 1.0	36.7 ± 1.5	36.5 ± 2.4	35.9 ± 2.1	36.2 ± 0.6
Vitamin E adjusted to 8.6 mmol C+T/L (μmol/L)	34.7 ± 0.1	33.7 ± 0.8	33.3 ± 1.0	34.7 ± 1.4	34.4 ± 1.1	34.3 ± 0.4
Vitamin C (μmol/L)	53.1 ± 0.4	49.0 ± 3.1	49.4 ± 4.1	46.5 ± 4.9	51.4 ± 4.3	48.7 ± 2.0 ³

¹ $\bar{x} \pm$ SD. C, cholesterol; T, triacylglycerol. To convert cholesterol values to mg/dL, multiply by 38.6.²80% β-carotene, 20% α-carotene.³Significantly different from survivors after means were adjusted for smoking habits and age, $P < 0.05$ (with Bonferroni correction for multiple comparisons).

cancer at any of the studied cancer sites. Those with fatal cancer were, on average, ≈ 10 y older than survivors. A higher percentage of smokers was observed in the lung (71%) and all cancer (47%) groups than in the survivors (32.5%). Mean plasma concentrations of vitamin C differed significantly between the all cancers and survivor groups. Lipid-adjusted vitamin E and retinol, as well as the mean plasma concentrations of these vitamins unadjusted for blood lipids, did not differ significantly between survivors and those who died from cancer at any of the cancer sites studied. With regard to the lipid-adjusted and unadjusted carotene concentration, significantly lower mean carotene values were observed in the lung, stomach, and overall cancer groups than in the survivors. Group means for plasma concentrations of carotene not adjusted for blood lipids and those adjusted for blood lipids did not differ significantly between survivors and those who died from cancer at any of the studied cancer sites. Lipid-adjusted mean retinol concentrations were slightly lower than the unadjusted means; lipid-adjusted group means for plasma concentrations of vitamin E were considerably lower than were the unadjusted values. Lipid-adjusted plasma vitamin E concentrations were lower than the unadjusted concentrations because they were adjusted to 8.6 mmol/L cholesterol plus triacylglycerol, which was lower than the corresponding mean values of survivors (9.5 mmol/L) and of those with fatal cancer at the sites considered (lung: 9.9 mmol/L; prostate: 9.4 mmol/L; stomach: 9.3 mmol/L; colon: 9.4 mmol/L; and all cancers: 9.6 mmol/L). The vitamin E values were reduced more by this adjustment than were the retinol or carotene values because of the stronger correlation of vitamin E concentrations with those of plasma lipids.

Risk analysis

The results of the analyses based on the Cox proportional hazards regression models are summarized in **Table 3**. Low plasma cholesterol concentrations (<5.16 mmol/L) were associated with a significantly higher risk of fatal lung cancer in study participants who were >60 y of age at baseline. This finding remained after exclusion of those who died during the first 2 y of follow-up. Low plasma cholesterol concentrations were related to an increased risk of prostate cancer in men >60 y of age at baseline. These findings were still significant after exclusion of those who died during the first 2 y of follow-up. The very wide CIs seem to be due mainly to the small number of deaths and give an inaccurate estimation of the risk. Plasma cholesterol concentrations below the first quartile were not associated with an increased

mortality risk from stomach cancer. Exclusion of those who died during the first 2 y of follow-up did not change this finding.

In study participants >60 y of age at recruitment, a significant negative association between low plasma cholesterol concentrations and colon cancer deaths was observed. This result remained significant after exclusion of those who died during the first 2 y of follow-up. Low plasma cholesterol concentrations were associated with a significantly increased risk of overall cancer mortality in individuals >60 y of age. This result remained significant after exclusion of those who died during the first 2 y of follow-up. With exclusion of the first 2 y of follow-up from the analysis, the relative risk estimates remained practically unchanged for lung cancer. The relative risk estimates decreased, however, for the prostate, colon, and all cancers groups after exclusion of the first 2 y of follow-up, but they remained significantly higher than those for survivors.

DISCUSSION

The principal result of the present analysis was the finding of an increase in total cancer mortality as well as in cancer mortality of the lung, prostate, and colon at low plasma cholesterol concentrations (<5.16 mmol/L, or <199 mg/dL) in men >60 y of age. These findings agree with the results of previous studies. A meta-analysis of 18 cohort studies showed a significantly increased risk of total cancer death in men (but not in women) with total cholesterol concentrations <160 mg/dL (4.15 mmol/L) compared with 160–199 mg/dL (4.15–5.16 mmol/L) (1). In the Framingham Study, serum cholesterol concentrations <160 mg/dL were associated with a significantly increased risk in male smokers but not in nonsmokers (13). Guize et al (14) found a slight tendency in study participants >65 y of age toward an inverse association between blood cholesterol concentration and cancer mortality, whereas in younger participants the association tended to be positive.

In addition, the aforementioned overview analysis by Jacobs et al (1) showed a nonsignificant inverse association of total blood cholesterol and lung cancer death in both men and women. More recently, the Rancho Bernardo cohort study showed that both men and women with baseline plasma cholesterol concentrations <160 mg/dL were more likely to die of lung cancer than were study participants with higher concentrations (24). This difference was significant in women. When smokers of the Multiple Risk Factor Intervention Trial (23) were divided into 2 groups on the basis of their serum cholesterol concentrations (≥ 4.14 compared with <4.14 mmol/L), the relative risk of lung



TABLE 3

Relative risks (RRs) and 95% CIs of low plasma cholesterol compared with higher concentrations adjusted for age, smoking, and plasma vitamin C, vitamin E, retinol, and carotene concentrations for various cancer sites: 17-y follow-up of the Basel study¹

Cancer site	Status of explanatory variables	Values for all cases (a)		Values, first 2 y of follow-up excluded (b)	
		RR	95% CI	RR	95% CI
Lung (a: n = 87; b: n = 83; c: n = 21; d: n = 19; e: n = 5; f: n = 5)	Low cholesterol and age > 60 y	1.99	(1.18, 3.37)	1.91	(1.11, 3.31)
	Low cholesterol and age ≤ 60y	0.54	(0.21, 1.38)	0.56	(0.22, 1.43)
Prostate (a: n = 30; b: n = 29; c: n = 8; d: n = 7; e: n = 1; f: n = 1)	Low cholesterol and age > 60 y	7.71	(1.45, 41.16)	6.41	(1.16, 35.38)
	Low cholesterol and age ≤ 60 y	0.28	(0.03, 2.31)	0.28	(0.03, 2.31)
Stomach (a: n = 28; b: n = 24)	Low cholesterol	1.70	(0.76, 3.81)	1.51	(0.62, 3.70)
Colon (a: n = 22; b: n = 21; c: n = 7; d: n = 6; e: n = 2; f: n = 2)	Low cholesterol and age > 60 y	4.07	(1.53, 10.83)	3.49	(1.25, 9.75)
	Low cholesterol and age ≤ 60 y	0.90	(0.20, 4.11)	0.91	(0.20, 4.17)
All cancers (a: n = 290; b: n = 276; c: n = 61; d: n = 53; e: n = 28; f: n = 28)	Low cholesterol and age > 60 y	2.08	(1.54, 2.82)	1.85	(1.34, 2.54)
	Low cholesterol and age ≤ 60 y	0.86	(0.57, 1.28)	0.90	(0.60, 1.35)

¹a, for all cases; b, cases with first 2 y of follow-up excluded; c, all cases with low cholesterol and age > 60 y; d, cases with low cholesterol and age > 60 y, first 2 y of follow-up excluded; e, all cases with low cholesterol and age ≤ 60 y; f, cases with low cholesterol and age ≤ 60 y, first 2 y of follow-up excluded. Low cholesterol is that below the first quartile, ie, <5.16 mmol/L. The age variable refers to age at baseline in 1971–1973.

cancer was 0.76 (95% CI: 0.64, 0.91) for those in the higher cholesterol group.

Similar to the findings of the present study, higher colon cancer risk in individuals with low cholesterol concentrations was observed in prior analyses (9, 29, 30). In the Framingham Study (27), colon cancer in men was inversely related to the serum LDL cholesterol fraction. Other studies did not show an association (23, 30–32), and there were also a few positive correlations (9, 33). With one exception (34), the results of the limited number of studies on stomach cancer, as in the present study, did not show an association (9, 15, 17, 30). Few studies have analyzed the risk of prostate cancer in association with low blood cholesterol concentrations (9, 15, 17, 30). The results of 2 of these studies (9, 30) agree with the increased risk found in the present study.

In summary, overall evidence of an increased cancer risk in individuals with low blood cholesterol is inconsistent and seems, as shown in the present study, to vary in different population subgroups. No standard definition of hypocholesterolemia was used. In general, it was defined by the total serum cholesterol concentration, and concentrations ≤4.15 mmol/L or lower than the lowest quintile, quartile, or tertile (values ≤223 mg/dL, or 5.78 mmol/L) (3, 39).

It is possible that the associations between low blood cholesterol concentrations and risk of cancer death are the consequence of confounding factors. Smoking is an important risk factor for cancer of various sites, and in several studies the excess risk of cancer was confined to smokers with low cholesterol concentrations (13, 16). However, smokers do not tend to have lower cholesterol concentrations than nonsmokers. Even though smoking lowers HDL cholesterol concentrations, this reduction is countered by a tendency for smokers to eat more saturated fat, thus raising their LDL cholesterol (3, 40). The inverse associations between serum cholesterol and cancer could also be secondary to the associations of the lipid-soluble vitamins E, retinol, and β-carotene with cancer (9, 26, 41–43). In the present study, as in others (9), plasma concentrations of these vitamins were correlated with plasma cholesterol concentrations (36). An inverse association between β-carotene and cancer risk (especially lung cancer) has been observed consistently in case-control and cohort studies (44). For vitamin E and

retinol the evidence is less clear (45). In addition, the results of intervention trials indicate that supplementation with β-carotene is of no benefit in the prevention of cancer (44).

In the present study, the associations between low plasma cholesterol and cancer mortality risk persisted after adjustment for smoking and plasma antioxidant vitamin concentrations, but residual effects of these factors and effects of unmeasured variables cannot be ruled out. The fact that these associations were only seen in older but not in younger study participants suggests that competing lethal risk may be an explanation (13). To counter this hypothesis, several studies have incorporated competing risk of death in life-table analyses of cancer death and cholesterol concentrations and have failed to find such an effect (3).

It can also be postulated that the observed associations are the result of preclinical cancer (39, 46). The fact that in the present study the association between low plasma cholesterol and cancer was only seen in older but not in younger study participants supports the hypothesis of a “preexisting cancer effect.” Cancer incidence is higher in older subjects; thus, preclinical cancer at baseline is more probable (Table 3).


In most studies, as in the present one, individuals have been classified according to a single cholesterol measure at baseline. Thus, the “low cholesterol” group is likely to include persons with genetically low concentrations as well as those with acutely or chronically depressed cholesterol as a result of inflammation, cancer, or other diseases (3, 39). In the early 1970s, when the baseline measurements of the present study were carried out, few people were treated with lipid-lowering drugs (47). The conflicting results of controlled clinical trials testing lipid-lowering drugs are therefore not discussed (48). A more recent study (30) tried to distinguish between permanently low and decreasing cholesterol concentrations. A significantly increased risk of cancer mortality was observed in men whose total cholesterol concentrations decreased within 6 y of observation but not in those with constant low cholesterol (30).

In most studies, the hypothesis that cholesterol concentrations are reduced by preexisting (ie, preclinical) cancer has been tested by analyzing the association between cholesterol concentration and cancer risk after the exclusion of cancer cases occurring dur-



ing the first few years of follow-up, expecting that the inverse association would decrease or disappear (48). In the present study, the relative risks for overall, colon, and prostate cancer mortality were attenuated after exclusion of mortality during the first 2 y of follow-up. Similar results were found in other studies when the first 2–5 y were excluded (9, 10, 12, 15, 23).

The unchanged lung cancer results in the present study and the persistently increased cancer risks in others (6, 13, 24, 29) suggest that exclusion of ≤ 10 y (49) of follow-up data might be necessary. Because of the small number of fatal cancer cases in the present study, it was not feasible to test whether the increased lung cancer mortality would persist if mortality during the first 10 y of follow-up were excluded from the analyses, as it did in the study of Zureik et al (47); that result was more consistent with a direct causal action of cholesterol than with inverse causality.

In conclusion, the negative association shown in the present study between mortality from cancer at various sites and low plasma cholesterol concentrations in men > 60 y of age is not the result of confounding by lipid-adjusted vitamin E, vitamin A, carotene, or vitamin C concentrations. The decrease in relative risks with exclusion of the first 2 y of follow-up, however, seemed to be attributable to the effect of preexisting cancer. But on the basis of our results, it is not possible to reject the hypothesis that low blood cholesterol increases the risk of cancer. The persisting significant associations with low cholesterol, especially of lung cancer, need further investigation. 

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