Changes in Plasma Lipid and Lipoprotein Cholesterol and Weight prior to the Diagnosis of Cancer

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ABSTRACT
Changes in lipoprotein cholesterol, total plasma cholesterol, and weight prior to the diagnosis of cancer were examined in 103 men who developed cancer in a cohort of 3805 type IIa hyperlipidemic men aged 35–59 enrolled in the Lipid Research Clinics Coronary Primary Prevention Trial. Study measurements were made bimonthly. After adjusting for the effects of the trial intervention and other determinants of lipid levels, the cholesterol levels of the cases diagnosed with nonlocalized cancer dropped below the expected level approaching diagnosis when compared to the entire study population. The decrease averaged 9.3 mg/dl and began about 2 years prior to diagnosis. Weight levels dropped an average of 1.2 kg over the same period. Weight and cholesterol were significantly lower than expected within 8 months of diagnosis (P < 0.05). No decrease was seen for those diagnosed with localized malignancies. Patterns for low-density lipoprotein cholesterol reflected those of total cholesterol. There was no clear relationship between cancer diagnosis and patterns of change for triglycerides and high-density lipoprotein cholesterol. In the future, investigations of any relationship between a host physiological state and cancer occurrence should account for the metabolic effects of preclinical disease demonstrated here. To protect against spurious conclusions, incident cases occurring within 2 years of measurement should be analyzed separately. In studies of cancer mortality, deaths occurring within 3.5 years of the base-line measurement should be analyzed separately.

INTRODUCTION
The report in 1974 by Rose et al. (1) of an inverse association between blood cholesterol level and the risk of cancer sparked a large body of epidemiological research. However, the likelihood that the relationship between low blood cholesterol and cancer risk is a causal one is difficult to evaluate given the inconsistency of the results (2–6). The question is of great potential public health significance because efforts are currently under way to lower blood cholesterol in a large proportion of the general population (7).

Establishing the temporal relationship between low cholesterol levels and the occurrence of cancer has been problematic. Several epidemiological investigations have found that the relationship between low blood cholesterol and cancer is strongest in the first 2 years following the base-line cholesterol measurement (6, 8–14). The implication is that cancer undetected at the base-line examination lowered blood cholesterol levels, a process that McMichael et al. (15) have termed a preclinical cancer effect. Not every epidemiological investigation has found a preclinical cancer effect, and in at least two reports, the inverse association between cholesterol and cancer has strengthened with increasing time from the base-line measurement (16, 17). Until the nature of the effect of cancer on cholesterol levels is better understood, other questions surrounding the cancer-cholesterol relationship cannot be validly addressed.

In the absence of repeated measurements of cholesterol preceding the diagnosis of cancer, evidence for the preclinical cancer effect is only circumstantial. Three studies have reported direct evidence for a reduction of blood cholesterol preceding cancer diagnosis: the Paris Prospective Study, the Multiple Risk Factor Intervention Trial, and the Framingham Study (8, 13, 18). In the first two studies, the cholesterol decreases were measured from the time before death from cancer rather than before diagnosis, so the possible cholesterol-lowering effect of cancer treatment cannot be separated from the effects of the cancer itself. The Framingham data are for cancer incidence rather than for cancer mortality. However, the interval between measurements was 2 years, so the data cannot address changes over shorter durations. In none of the studies were measurements of lipoprotein cholesterol subfractions available.

This paper examines the preclinical cancer effect in a study population with both cancer incidence data and frequent cholesterol measurement (every 2 months), the Lipid Research Clinics Coronary Primary Prevention Trial. The CPPT was a multicentered, double-blinded, placebo-controlled trial of the bile acid sequestrant cholestyramine among type IIa hypercholesterolemic men, i.e., men with elevated total serum cholesterol due to low-density lipoprotein cholesterol. The trial tested the hypothesis that long-term reduction of serum cholesterol leads to a lowered incidence of coronary heart disease. In addition to total plasma cholesterol, high-density lipoprotein cholesterol, triglyceride, and weight were also measured bimonthly.

MATERIALS AND METHODS
Study Population. The study population, the design, and the results of the CPPT have been described in detail elsewhere (19–22). Briefly, between November 1973 and July 1976, 3806 men aged 35–59 with type IIa hyperlipidemia were randomized into two groups: one received the resin cholestyramine and the other an inert placebo. Type IIa hyperlipoproteinemia was defined as a total cholesterol level in excess of 265 mg/dl, a low-density lipoprotein cholesterol in excess of 190 mg/dl, and a fasting triglyceride level of less than 300 mg/dl. For this analysis, the study follow-up period ended April 30, 1983. The median follow-up time from randomization to the end of the study period was 7.6 years.

Among the exclusion criteria were the presence of conditions predisposing to coronary heart disease (e.g., moderate to severe hypertension, obesity, or diabetes mellitus), secondary hyperlipoproteinemia, or any potentially life-shortening disease. Enrollees were free of clinically apparent cancer. Moreover, as part of the exclusion concerning life-shortening disease, a history of any cancer, except for basal cell carcinoma of the skin, was grounds for exclusion. One randomized partici-
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A participant was found to have had a history of cancer and is excluded from all analyses reported here. During the prerandomization phase of the trial, every participant was prescribed a diet designed to lower his total cholesterol level 3–4%. Those participants whose LDL-C levels fell below 175 mg/dl after the dietary intervention were excluded from the trial. Study Measurements. For the duration of the trial, participants were asked to visit the clinic at which they were randomized every 2 months. Once a year, a physical examination and detailed medical history were done, including questions concerning smoking and drinking habits.

At each visit, fasting plasma cholesterol, HDL-C, triglyceride levels, and weight were measured. Using the approximation that very low-density lipoprotein cholesterol is one-fifth the level of fasting triglyceride, LDL-C was estimated at most visits as a function of total cholesterol, HDL-C, and triglyceride level (23). At one visit per year, LDL-C was determined directly. All aspects of the lipid and lipoprotein determinations were rigidly standardized with quality control over time so that lipid determinations at the 12 participating clinics would be comparable (24, 25). Participant adherence to the study regimen was also monitored at each visit. Participants were asked to bring in any study medication they had not taken since their previous visit. Adherence was measured in units of packets of medication taken per day, by counting the amount of unused drug, and noting the elapsed time since the previous visit.

At the end of the trial, the vital status of every participant was known. Seventy years after randomization approximately 86% of the participants were still attending clinic visits.

Case Ascertainment and Definition. Cancer cases were identified from the coordinating center files of the trial. The coordinating center routinely collected information regarding all hospitalizations for any reason during the trial. Two of the authors (S. B. K. and D. L. M.) reviewed all incident cancer cases ascertained during the trial. In addition, all deaths, and all hospitalizations for either benign neoplasms, unspecified neoplasms, or for procedures commonly used to diagnose cancers were reviewed to identify cases that might have been inadvertently overlooked. A case was defined as any trial participant who had a pathology report, discharge summary, or death certificate mentioning the existence of a malignant neoplasm (ICD-9 rubrics 140–208), excluding nonmelanotic skin cancer, during the CPPT. Tumors that were designated by pathology as only suspicious for cancer were not regarded as cancer. Tumors were also classified according to localization. Extensive disease was defined as any tumor that had any regional or metastatic spread or any leukemia or lymphoma. The determination was based on positive clinical or pathological evidence of spread. Cases who were not staged were considered to have localized disease.

Statistical Methods. The analysis focused on patterns of deviations from predicted cholesterol levels among the cancer cases by time interval prior to diagnosis: the deviation from predicted is the observed minus the predicted level. For each trial participant, at every measurement point throughout the trial, a predicted cholesterol level was calculated by using a linear model (described below). We then averaged the cases' deviations by time intervals preceding the diagnosis of the tumor. The method is an extension of the serially additive expected dose model introduced by Smith et al. (26) and described elsewhere (27). If cancer causes a reduction in cholesterol, the blood cholesterol level should become progressively lower than predicted approaching a cancer diagnosis. Thus, the deviations for cases occurring at different times during the trial and in different treatment groups could be combined. The models varied depending upon the time into the trial that the measurement was made. The model for years 2 through 7 postrandomization included terms for age, the average of the previous six measurements of the lipid or weight level, the base-line lipid or weight level, the year of randomization, the clinic of randomization, the average number of cigarettes smoked per day, any change in smoking or drinking status during the previous year, any change in average alcohol consumption in the previous year, the month of lipid/weight measurement, and the average body mass index ($kg/m^2$) over the previous six visits. In both groups, the amount of study medication taken was also included, and in the cholestyramine group, drug-smoking and drug-drinking interaction terms were included. During the first year of the trial no previous lipid or weight measurements other than base-line measurements were included in the models. After the seventh year of the trial, there were too few participants to support the large number of independent predictors, so a reduced model including only age, the mean of the six previous measurements of lipid or weight, the base-line level, and the dose of drug taken were included. The models are summarized in Table 1.

Independent variables were selected either to increase the precision of the prediction of HDL-C, LDL-C, triglyceride, or weight levels, or to control confounding (e.g., change in smoking and change in drinking). For example, in Doll and Hill’s study of smoking and cancer (29), subjects who had recently quit smoking were at elevated risk of death from lung cancer compared to continuing smokers. It could be that they quit to obtain relief from symptoms of advanced, undiagnosed disease. Such a change in smoking behavior could also lower cholesterol levels (30). A drop in cholesterol observed before diagnosis could reflect either the preclinical cancer effect or the effect of smoking cessation.

After estimating a cancer case's predicted level, his deviation from predicted was calculated for each 4-month prediagnostic interval. If a case had more than one measurement in an interval his deviations were averaged. The deviations were then averaged across cases by prediagnostic interval. For example, all of the cases' deviations from within 4 months of their diagnosis were used to calculate the mean deviation of the first prediagnostic interval. All deviations measured between 4 and 8 months made up the second prediagnostic interval, etc. In each prediagnostic interval, the 95% confidence interval was calculated as $1.96 \times \text{SEM}$ of the deviations. Analyses were performed for all cases and after stratification by extent of disease.

For all of the total cholesterol analyses, one measurement of 711 mg/dl was deleted as an outlier for a member of the treatment group. This was over 300 mg/dl higher than any other previous measurement, and the man's triglyceride, HDL-C, and LDL-C were not remarkably different from any other previous measurement. After stratification by extent of disease, the deviations measured between 4 and 8 months were used to estimate the mean deviation for cases with localized disease.

<table>
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* Variables 4–19 and 21–32 are indicator variables; all others are continuous variables.

$P$ indicates placebo group; $C$ indicates cholestyramine group; $x$ indicates variable included in model; and 0 indicates variable not included in model.

Mean of previous 6 body mass indices not included in models for weight as dependent variable.
elevated. In addition, three men had triglyceride measurements set to missing because of levels above 1000 mg/dl. Since LDL-C estimates often depended on the triglyceride measurement, the corresponding LDL-C levels were also set to missing.

RESULTS

Table 2 presents the characteristics of the study population and of those diagnosed with cancer during the trial. Cases and noncases were similar at base line, although cases tended to be older. Surprisingly, cases were neither more likely to have been smokers nor to have consumed more alcohol than the noncases. Pathological confirmation was available for 71% of the 106 primary malignant neoplasms documented during the trial, excluding nonmelanoma skin cancer. Three of the cases attended no visits after randomization and will not be considered further (sites: bladder, kidney, and larynx). Table 3 lists the site distribution of the 103 cases used in this analysis.

In Fig. 1, which presents the mean deviations from predicted cholesterol level by prediagnostic interval for the cancer cases, each point on the graph represents the mean difference between the observed and predicted cholesterol level in consecutive 4-month intervals preceding the diagnosis of cancer. The date of diagnosis was taken to be the date of a positive biopsy. In the absence of a pathology report, it was the date that some documentation first referred to the cancer as malignant. The rightmost point along the abscissa is the mean deviation from expected cholesterol level for those diagnosed approaching the diagnosis of cancer. The point to its left is the mean deviation from expected for measurements more than 4 but less than 8 months prior to diagnosis, and so forth. The 95% confidence bands were derived by constructing 95% confidence intervals around each point and then connecting the upper and lower bounds of the intervals. The confidence intervals should be interpreted primarily as indicators of measurement precision. They should be interpreted as hypothesis tests only cautiously, given the large number of comparisons reported. Points were not plotted if fewer than 10 cases contributed information to the interval.

In general, there is no clear association between cholesterol level and the diagnosis of cancer (see Fig. 1). The largest mean difference was for the interval just after 6 years prior to diagnosis, when the cases were 6.8 mg/dl lower than expected. There is no strong evidence of a reduction in cholesterol level approaching the diagnosis of cancer. Fig. 2 shows the mean deviation from expected cholesterol level for those diagnosed with extensive disease. Here there is evidence of a decrease in cholesterol level associated with the diagnosis of cancer, with a 9.3 mg/dl decrease from the 16- to 20-month interval to the first interval prior to diagnosis. Just prior to diagnosis, the cases' plasma cholesterol averaged 6.4 mg/dl below predicted (95% confidence interval, 0.2, 12.9).

![Mean difference from predicted plasma cholesterol level for cancer cases by time preceding diagnosis (with 95% confidence bands).](image)

The mean deviations from predicted cholesterol levels for those diagnosed with local disease are shown in Fig. 3. There is no evidence for a decrease in cholesterol levels approaching diagnosis. There are, however, two occasions of significantly lower than expected cholesterol levels, in the 72- to 74-month interval and in the 28- to 32-month prediagnostic intervals.

The patterns of LDL-C are similar to those for total cholesterol (data not shown). Among the extensive disease group,
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There is evidence for a decrease in LDL-C within 20 months of diagnosis as there was for total cholesterol. There was not a clear pattern for either HDL-C or triglyceride (data not shown). For HDL-C, the mean deviation was never more than 1.3 mg/dl from predicted. The deviations from predicted triglyceride level were erratic and conformed to no obvious pattern.

The mean deviations from predicted weight for those with extensive disease are shown in Fig. 4. The patterns of weight deviations are very similar to those for total cholesterol. The cases' weights were below predicted between 6 and 7 years prior to diagnosis. Within 4 months of diagnosis, their weight was 1.2 kg lower than predicted, while between 16 and 20 months of diagnosis, their weight was 0.1 kg lower than predicted.

DISCUSSION

The results indicate that there is a decrease in plasma cholesterol levels associated with cancer apparent within 20 months of diagnosis in patients diagnosed with nonlocalized disease. No decrease approaching diagnosis is seen in those diagnosed with localized disease. Of the lipoprotein fractions, LDL-C most clearly reflects the decrease in total cholesterol. The role of HDL-C and triglyceride in explaining the overall pattern of total cholesterol change is less clear.

A loss in body weight is also seen prior to diagnosis. Its pattern closely resembles that of the decrease in plasma cholesterol levels. Whether the lipid decrease is secondary to the loss of weight or whether the lipid and weight decreases are manifestations of the same underlying metabolic process was not addressed with these data.

There are two reasons to believe that the decrease in weight and cholesterol are related to progressing disease. (a) Extensive disease is associated with the observed effect while nonextensive disease is not, so the presence of a tumor is not sufficient to cause the effect; (b) studies of cholesterol and cancer using cancer mortality as an end point, and studies of cholesterol levels after cancer diagnosis, tend to show even lower cholesterol levels, suggesting a process that is continuing over time (13, 31, 32).

The physiological reasons for the decrease are a matter requiring further investigation. Studies have found increased LDL-C catabolism in patients with prostate cancer, and some malignant cells have been shown to have increased LDL receptor activity (33-35). A host response to a progressing tumor mediated by a substance such as tumor necrosis factor may be involved (36, 37). Physiological responses to tumor necrosis factor include anorexia, cachexia, and disturbances in lipid metabolism (36). Two serum growth factors, human mononuclear colony-stimulating factor and human granulocyte-macrophage colony-stimulating factor, have both been shown to lower blood cholesterol (38, 39). It is not known whether these substances are found at elevated levels in those with extensive disease but not localized disease. Recently, Ueyama et al. (40) have shown that cells from a patient's gallbladder cancer tumor secrete in culture a substance that stimulates LDL receptor activity in normal fibroblasts from other individuals.

The decreases in total cholesterol levels prior to cancer diagnosis seen in the CPPT participants with extensive disease are similar to decreases observed by Sorlie and Feinleib (18) using data from the Framingham cohort and Sherwin et al. (13) using MRFIT data. Fig. 5 compares the adjusted cholesterol decreases of the CPPT cases with extensive disease with male cases from the other two studies. The data from MRFIT were
and triglyceride. The significance of these reductions is unclear.

There are similarly timed reductions in LDL-C. Hence, cancer would lower serum cholesterol compared to decreases found in less selected populations. If, as part of the explanation for the high cholesterol levels in these studies is the presence of a defective LDL receptor gene (as in familial heterozygous hypercholesterolemia), and tumors lower cholesterol by inducing LDL receptors in non-tumor cells, then those with an LDL receptor defect would be expected to show only one-half the response of those with both genes intact. Hence, cancer would lower serum cholesterol less in groups selected because of high cholesterol levels. The changes found in these two studies may be damped compared to decreases found in less selected populations. If, for instance, part of the explanation for the high cholesterol levels in these studies is the presence of a defective LDL receptor gene (as in familial heterozygous hypercholesterolemia), and tumors lower cholesterol by inducing LDL receptors in non-tumor cells, then those with an LDL receptor defect would be expected to show only one-half the response of those with both genes intact. Hence, cancer would lower serum cholesterol less in groups selected because of high cholesterol levels.

The total cholesterol level from 6 to 7 years prior to diagnosis is lower than expected in both extensive and nonextensive disease groups and in both treatment arms (data not shown) (4). There are similarly timed reductions in LDL-C, weight, and triglyceride. The significance of these reductions is unclear. Many of the measurements in these prediagnostic intervals are from the first year of the trial. Both randomization groups experienced an increase in triglyceride levels and a decrease in LDL-C and total cholesterol levels in the first year of the trial (22). The decrease in LDL-C in the placebo group is probably attributable to a combination of a regression to the mean effect and the effect of a cholesterol-lowering diet prescribed to all trial participants. In addition to these effects, the active treatment group took cholestyramine. The diet was one high in polyunsaturated fat designed to lower cholesterol levels 3 to 4% (19). It could be that "overresponders," detected by having a greater than average drop in cholesterol in the early trial period, were at greater risk of developing cancer. This hypothesis can be tested by examining cases detected after the conclusion of the trial, since they should also show this exaggerated lipid decrease early in the trial.

The question of greatest health concern is whether or not lowering blood cholesterol levels will increase the risk of cancer. The most direct evidence to address this question comes from clinical trials of cholesterol-lowering interventions. The present analysis was not designed to address this issue, but a report of the long-term health consequences of trial participation is in preparation. For several reasons, cardiovascular disease trials have a limited ability to answer the question: most were not designed to examine cancer end points, or were too small to have enough power to convincingly answer the question, or did not follow study subjects long enough to accommodate a reasonable disease latency period in the data analysis. As recently reviewed by Lackner et al. (42), the clinical trial evidence, despite its deficiencies, does not support the hypothesis that lowering cholesterol will increase cancer risk.

In epidemiological studies that account for a preclinical cancer effect in the analysis, the evidence for a relationship between low cholesterol and cancer is inconsistent (4). In most epidemiological studies, when an increase in cancer risk is observed with decreasing cholesterol levels, the relationship is usually seen only below about 195 mg/dl (43). The epidemiological data suggest, therefore, that reducing high cholesterol to this level would not be expected to increase the risk of developing cancer.

The absence of a consistent relationship makes a direct causal role for low cholesterol in the etiology of cancer difficult to support. Several authors have suggested that the low cholesterol-cancer association may be secondary to an inverse relationship between fat-soluble antioxidants or vitamins and cancer (44-48). Blood levels of many of these fat-soluble substances are strongly correlated with levels of blood cholesterol (44, 48-50). This hypothesis remains to be satisfactorily tested.

The results of the study indicate that from about 2 years prior to cancer diagnosis, lipid metabolism is affected for those who are eventually diagnosed with extensive disease. Researchers attempting to relate physiological measurements with the occurrence of cancer need to be mindful of the possible effects of preclinical disease. To protect against spurious conclusions, incident cases occurring with 2 years of measurement should be analyzed separately. In studies of cancer mortality, deaths occurring within 3.5 years of the base-line measurement should be analyzed separately.

REFERENCES
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